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"Anti-inflammatory and anti-allergic properties of flavonoids", Gabor M., Prog Clin Biol Res 213:471-480, 1986.

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"influence of h. pylori (hp) infection and/or low dose aspirin on gastroduodenal ulceration in patients treated with placebo, celecoxib or nsaids", goldstein et al., Gastroenterology, 1999, vol. 116, no. 4 part 2, pp.a174

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● G0756

CORRELATION OF *HELICOBACTER PYLORI* GENOTYPE WITH CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF INFECTED CHILDREN.

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H. pylori (*Hp*) strains isolated from adults have significant genetic heterogeneity. Specific *Hp* genes (*cag*A, *vac*A, *ice*A) are found in more virulent strains and are associated with increased gastroduodenal disease severity in adults. The presence of these *Hp*-virulence genes and their association with gastroduodenal disease in children was not known. Our pilot study evaluated pediatric *Hp* isolates from different geographic regions to determine if there was an association of *Hp* virulence genes with severity of gastroduodenal disease. Diagnostic EGD for gastrointestinal complaints was performed on children at participating centers. Endoscopic diagnoses were recorded and the updated Sydney system was used to determine histopathology on gastric biopsies. DNA isolation was performed on primary *Hp* cultures and molecular analysis was performed by reverse hybridization line probe assay (LiPA) and type-specific PCR. One *Hp* isolate from each of the 18 different patients was analyzed. The mean age of patients was 11 yrs. (range 3–16 yrs.); 61% male. All 18 children had gastritis of varying severity; 8 (44%) had gastric and/or duodenal ulcers. A significant degree of genetic heterogeneity was observed in these pediatric *Hp* isolates. Three children had *Hp* strains that were similar in *vac*A-s, *vac*A-m and *cag*A genes; all 3 children were of Hispanic origin. Two strains with *vac*A-s1c genotype were obtained from second generation Asians living in Canada supporting an association of this genotype with people of East-Asian descent. Of 8 children with ulcers, 6 (75%) had *Hp* strains that were *cag*A (+) and 2 (25%) that were *cag*A (-). All s2/m2 *Hp* strains were *cag*A (-) suggesting an association between s1 and *cag*A positivity. Of the 5 strains with multiple signals in *vac*A s, 4 showed multiples in *vac*A m; suggesting mixed strains. In our study, pediatric *Hp* strains containing *vac*A s1, *cag*A, and *ice*A1 were not completely predictive of disease severity. Children appear to be initially infected with multiple *Hp* strains that are genetically diverse. We postulate that over time, bacterial and host factors may play a role in the selection of the predominant *Hp* genotype and eventual disease outcome.

● G0757

EVALUATION OF THE TESTPACK PLUS™ *H. PYLORI* TEST FOR DETECTION OF HUMAN IGG ANTIBODIES TO *H. PYLORI* IN VENOUS WHOLE BLOOD (WB), SERUM, PLASMA, AND FINGERSTICK WB.

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In symptomatic patients with dyspepsia, serologic testing for *Helicobacter pylori* (HP) is the test of choice for initiating a "test and treat" strategy. The objectives of these multicenter studies (5 sites) were to evaluate the performance (sensitivity and specificity) of the new, rapid TestPack® Plus™ *H. pylori* assay to detect IgG antibodies specific to HP, as compared to (1) the reference methodology (culture and /or histology & CLOtest®) and to a quantitative commercially available Enzyme Immunoassay (EIA) in symptomatic patients (pts) (n = 242 from 4 sites, (2) to assess the performance of the new assay using WB specimens from symptomatic pts (n = 107 of the 242 at 2 of the 4 sites), and (3) to evaluate the performance of the new assay using matched serum, plasma, venous WB, and fingerstick WB specimens collected from 200 asymptomatic, healthy volunteer donors at a single site. The 242 symptomatic pts enrolled (112 M., 130 F; mean age ±SD: 49.7±14.3 M and 47.5±13.4 F) had no PMHx of specific anti-HP Rx and had not received antibiotic treatment four weeks prior to testing. RESULTS: (Objective 1): as compared to the reference methodology, the sensitivity and specificity of the TestPack®. Plus™ *H. pylori* assay was 88.5% (123/139) and 84.9% (84/99), respectively. Four specimen results interpreted as indeterminate (IND) by the reference methodology were not included in these calculations. Of the fifteen specimens seropositive by the new assay and negative by the reference methodology, all tested positive with the EIA, HM-CAP™. The relative performance of the TestPack® Plus™ *H. pylori* was also evaluated against an EIA HM-CAP standard. The relative sensitivity and specificity of the TestPack® Plus™ *H. pylori* was 88.2% (135/153) and 95.2% (80/84), respectively. This comparison had 5 different specimen results interpreted as IND by the HM-CAP™ assay which were excluded from the calculations. (Objective 2): For the 107 subset pts, a comparison between TestPack® Plus™ *H. pylori* assay results using matched serum and venous WB was performed with an overall agreement of 94.4% (101/107). (Objective 3): As compared to serum from asymptomatic healthy volunteers, matched specimens (plasma, venous WB, and fingerstick WB), performance with the TestPack® *H. pylori* assay was equivalent and no statistically significant difference (p = 0.51) was observed. CONCLUSIONS: The TestPack® Plus™ *H. pylori* assay performs well as compared to the "gold standard" reference methodology and, as compared to MH-CAP™. TestPack® Plus™ *H. pylori* assay shows no significant difference in results when using serum, plasma or WB (venous or fingerstick) specimens. This research was made possible by a grant provided by Abbott Diagnostic Division.

● G0758

CELECOXIB IS ASSOCIATED WITH A SIGNIFICANTLY LOWER INCIDENCE OF CLINICALLY SIGNIFICANT UPPER GASTROINTESTINAL (UGI) EVENTS IN OSTEOARTHRITIS (OA) AND RHEUMATOID ARTHRITIS (RA) PATIENTS AS COMPARED TO NSAIDS.

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Cyclooxygenase-2 inhibition (COX-2) mediates the anti- inflammatory effects associated with NSAIDs, whereas inhibition of COX-1 appears to be responsible for their UGI adverse effects. The purpose of this analysis was to assess the relative UGI safety of celecoxib, a specific COX-2 inhibitor as compared to NSAIDs by examining clinically significant UGI events such as perforation, bleeding and gastric outlet obstruction across 14 controlled double blind trials of RA and OA patients. A total of 11,007 patients (pts) were enrolled and received: placebo (n=1864), celecoxib in doses ranging from 25 to 400 mg BID (n=6376) or an NSAID (n=2768); naproxen 500 mg BID, diclofenac 50–75 mg BID, or ibuprofen 800 mg TID for 2 to 24 weeks. All potential events were evaluated by an independent external review committee (first 3 authors above). The committee developed a priori definitions of what were considered to be clinically significant UGI events and then determined without unblinding whether the patens had an UGI perforation, UGI bleeding or gastric outlet obstruction. RESULTS: Of 101 potential events referred to the committee, 11 were clinically significant UGI events. The table presents the clinically significant UGI events expressed as an annualized incidence. As per the table, NSAIDs were associated with an excess risk of 1.48% for clinically significant UGI events (95% CI: 0.35%-2.62%) compared to celecoxib. In contrast, there was no excess risk with celecoxib vs. placebo (95% CI: -0.08% to 0.47%). Nine clinically significant UGI events were UGI bleeding episodes: 2 celecoxib pts, 3 naproxen pts, 3 diclofenac pts and 1 ibuprofen pts. The other 2 events were gastric outlet obstructions, both in pts receiving naproxen. CONCLUSION: Based on this large data set, these results demonstrate that the incidence of clinically significant UGI events with the specific COX-2 inhibitor, celecoxib and significantly less than NSAIDs and not different from placebo This research was funded by Searle.

	Placebo	Celecoxib	NSAIDs
Number of clin. sign. UGI events	0	2	9
Patient-years of exposure	208	1020	535
Annual Incidence	0%	0.20%	1.68%

*p<0.05 vs other treatments

● G0759

INFLUENCE OF *H. PYLORI (HP)* INFECTION AND/OR LOW DOSE ASPIRIN (AASA) ON GASTRODUODENAL ULCERATION IN PATIENTS TREATED WIGH PLACEBO, CELECOXIB OR NSAIDS.

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The effect of *Hp* infection on the development of NSAID-induced gastroduodenal ulcers (GDUs) remains controversial. Furthermore, many patients (Pts) use low dose ASA (≤325 mg/D) for CV protection. The purpose of this analysis was to evaluate the influence of *Hp* infection and/or low dose ASA on the incidence of GDUs in pts receiving placebo (P), a specific COX-2 inhibitor, celecoxib (C,50–400 mg BID), or an NSAID: naproxen (N,500 mg BID), ibuprofen (I, 800 mg TID) or diclofenac (D,50–75 mg BID). METHODS: Data for this pooled analysis were obtained from 4 independent double-blind 12-wk endoscopic trials in osteo-and rheumatoid arthritis pts. Pts using low-dose (ASA) were excluded from the *Hp* analysis. *Hp* negative pts were used to assess the effect of low dose ASA. *Hp* status was determined by CLOtest® at week 12. Only pts with no GDU on baseline EGD were enrolled in the studies. Ulcers were defined as ≥ 3 mm diameter with depth. RESULTS: Table 1 shows the incidence of GDUs for P, C, and NSAIDs as a function of *Hp* status (Analysis A) and for low dose ASA in *Hp* negative pts (Analysis B). It is interesting to note that in *Hp* negative, non-ASA users, the incidence of GDUs was 2.2%. CONCLUSION: Our large scale, prospective analysis suggests that *Hp* or low-dose ASA do not strongly influence the incidence of GDUs in pts receiving NSAIDs. In contrast, pts receiving celecoxib or placebo, low-dose ASA appears to be more strongly associated with GDUs than does *Hp* positive status. This research was supported by Searle.

Table 1	Ulcer Incidence % (pts with ulcers/total pts)		
Analysis A	Ulcers/Hp (+)	Ulcers/Hp(-)	OR (95% CI)
Placebo	7.1% (3/42)	2.2% (3/139	3.5 (0.62, 19.5)
Celecoxib	8.0% (18/226)	5.1% (42/831)	1.6 (0.90, 2.84)
NSAIDs	28.4% (52/183)	20.0% (137/686)	1.6 (1.10, 2.30)
Analysis B	Ulcers/ASA (+)	Ulcers/ASA (-)	OR (95% CI)
Placebo	10.0% (2/20)	2.2% (3/139)	5.0 (0.63, 32.4)
Celecoxib	10.4% (11/106)	5.1% (42/831)	2.2 (1.04, 4.23)
NSAIDs	22.2% (24/108)	20.0% (137/686)	1.1 (0.69, 1.84)

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Natural Treatment of Perennial Allergic Rhinitis.

Author/s: Stacy M. Thornhill

Abstract

Perennial allergic rhinitis is an IgE-mediated **inflammatory disorder** of the nasal mucosa characterized by paroxysms of sneezing, nasal congestion, pruritis, and rhinorrhea. The condition may be caused by certain environmental agents, food sensitivities, structural abnormalities, metabolic conditions, or synthetic drugs. Recent health impairment outcome studies on allergic rhinitis sufferers reveal a measurable decline in physical and mental health status and the inability to perform daily activities. Antihistamines, decongestants, anticholinergic agents, and corticosteroid drug therapy, alone or in combination, are typically used in the treatment of allergic rhinitis. Reported adverse side effects include sedation, impaired learning/memory, and cardiac arrhythmias. Therapeutic strategies should seek to decrease the morbidity already associated with this condition. Urtica dioica, bromelain, quercetin, N-acetylcysteine, and vitamin C are safe, natural therapies that may be used as primary therapy or in conjunction with conventional methods.

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Introduction

Allergic rhinitis is the most common allergic **disorder** in the United States, affecting 10-20 percent of the population.[1,2] The condition is characterized by continuous or periodic nasal congestion, rhinorrhea, sneezing, pruritis of the conjunctiva, nasal mucosa and oropharynx, allergic shiners, lacrimation, and fatigue. Predisposing factors are a positive family history of similar symptoms and a personal history of collateral allergy manifested as eczematous dermatitis, urticaria, and/or asthma. Clinical presentation may include nasal polyps, pale and boggy (sometimes reddened or excoriated) nasal passages, congested and edematous conjunctiva, injected pharynx, and swelling of the turbinates and membranes of the ear. Often, there is a temporal relationship between an allergen exposure and an acute episode of allergic rhinitis. Environmental agents that can cause this condition are dust mites, feathers, animal dander, mold, pollen, grass, and fungus spores. Many people with allergic rhinitis are also allergic to certain foods and may experience symptoms as a result of eating allergy-triggering substances in such foods as eggs, nuts, fish, shellfish, dairy products, or wheat.[3] In the absence of nonspecific stimuli in the history, structural abnormalities of the nasopharynx, exposure to irritants, upper respiratory infection, pregnancy with prominent nasal mucosal edema, prolonged use of alpha-adrenergic agents, or use of rauwolfia, beta-adrenergic antagonists, or estrogens should be excluded.

Pathophysiology

Most cases of allergic rhinitis are due to an indeterminate, yet specific, allergen-reagin reaction in the nasal mucosa. The immediate-response phase consists of an allergen binding to the IgE component of the mast cell. This initial pathophysiological event results in recruitment of numerous chemoattractants and **inflammatory** mediators, which signal eosinophil, basophil, neutrophil, and

monocyte infiltration.[4] Usually 2-8 hours after exposure to the antigen (delayed-response phase), there is intense infiltration of tissues with **inflammatory** mediators as well as tissue destruction in the form of mucosal epithelial cell damage, as there exists a perpetual mediator response (Figure 1). This late or delayed inflammation is associated with an increased sensitivity to the allergen after repeated exposures and a hyper-responsiveness to irritants or certain pharmacologic agents.

[Figure 1 ILLUSTRATION OMITTED]

While mast cells are widely distributed throughout the human body, they are found in high concentrations in the blood vessels of the sub-epithelial connective tissue of the respiratory tract and conjunctiva. Mast cell degranulation accounts for approximately one-half the symptoms of allergic rhinitis. Histamine, the principal **inflammatory** mediator in allergic rhinitis, is released by mast cells in the immediate-response phase and by basophils in the delayed-response phase. Histamine binding to H1-receptors has several consequences; it increases vasodilation, capillary permeability, and smooth muscle contraction, manifesting as rapid fluid leakage into the tissues of the nose as well as swollen, secretory nasal linings.[2]

Discussion

Antihistamines comprise the largest group of drugs on the market. Their effect is based on the blockade of [H.sub.1] histamine receptors located on the nasal vasculature and nerve endings.[5] Structural differences between the various drugs account for the differences in the potential side effects. The first-generation antihistamines contain ethylamine moieties that make them highly lipophilic and readily able to cross the blood-brain barrier.[5] This characteristic partly explains the numerous adverse effects associated with sedating antihistamines, including dizziness, tinnitus, cardiac arrhythmias, gastrointestinal distress, lassitude, incoordination, blurred vision, diplopia, euphoria, and tremors. In fact, it has been reported the first-generation antihistamines cause discernible drowsiness in 25 percent of adults.[6] Even in the absence of sedation, they can substantially impair thought processes and the ability to drive or operate machinery.

The piperazine- or piperidine-like structures of the second-generation antihistamines do not cross the blood-brain barrier and have not been found to cause significant sedation, fatigue, or anticholinergic effects. However, astemizole and terfenadine can cause torsades de pointes (a potentially fatal cardiac arrhythmia) if given concurrently with macrolides (erythromycin and troleandomycin), imidazole antifungals (ketoconazole and itraconazole), or to a person with liver disease. Drug interactions are also suspected with certain antidepressants and HIV-specific protease inhibitors.[6]

Topical decongestants reduce airflow resistance by attenuating the blood volume in the nasal mucosa. While selective in their action, these drugs are not effective for long-term use (defined as greater than one week) because of the risk of rebound hyperemia, receptor desensitization, mucosal damage, or ultimately, rhinitis medicamentosa, an excruciatingly painful condition of the nasal

passages.[6] Oral decongestants are likely to create more adverse systemic effects, including cardiac arrhythmias, hypertension, and CNS disturbances. They are contraindicated in individuals with heart disease, hyperthyroidism, glaucoma, or diabetes mellitus.

Anticholinergic agents control the vasodilation and secretion of serous glands in the nasal mucosa. Reportedly, these drugs can affect visual perception, reaction time, coordination and memory. In fact, the U.S. Food and Drug Administration ruled in 1985 that anticholinergics were not suitable (i.e., safe and effective) for over-the-counter distribution.[6]

Intranasal corticosteroid treatment has local side effects, including nasal irritation and bleeding and septal perforation. Their mechanisms of action involve modification of gene expression, formation of cell-regulatory proteins, and inhibition of **inflammatory** mediators.

A recent study by Marshall et al reveals a significant impairment in verbal learning, decision-making speed, and psychomotor speed in those who suffer from allergies. The end result is either frequent absenteeism from work or substantial decreases in productivity at work.[7] A nationwide study using the SF-36 and RQLQ questionnaires revealed rhinitis patients are tormented by repeated nose blowing, have a disrupted sleep pattern, are fatigued, and have a reduced ability to concentrate.[8] Taking drugs (prescription or over-the-counter) that further decrease the quality of life already imposed by allergic rhinitis should be avoided. Fortunately, there are certain nutrients and botanical medicines that can provide primary therapy or be used in combination with conventional methods.

Botanical and Nutritional Therapies for Allergic Rhinitis

Urtica Dioica (Stinging Nettle)

Histamine, serotonin (5-hydroxytryptamine), and acetylcholine are concentrated in the fresh stinging hairs on the leaves of nettle species.[9,10] Urtica also contains glucoquinones and chlorophyll. While there is no known botanical substance whose mechanism is inherently the same as that of antihistamines for treating allergic rhinitis, the recent development of biomechanical preservation by freeze-drying allows Urtica dioica to work in similar ways to its allopathic antihistamine counterparts.

A randomized, double-blind study using 300 mg freeze-dried Urtica dioica in the treatment of allergic rhinitis found 69 patients who completed the study rated it higher than placebo in global assessments: 58 percent rated it effective in relieving their symptoms and 48 percent found it to be equally or more effective than their previous medicine.[11]

Since antihistamines are used in allergic rhinitis to antagonize histamine, acetylcholine, and serotonin, it appears contradictory that a plant containing these mediators is used to treat allergic rhinitis. However, histamine also acts as an autocoid (a local hormone) to modulate the immune response.[12] Subcutaneous

and intravenous injections of histamine have been used effectively to treat numerous allergic conditions including headaches, migraine, cluster headache associated with vasomotor rhinitis, penicillin reaction, allergic arthritis, and cold urticaria with associated anaphylaxis.[13] It has been shown that an acute allergic response did not correlate with high plasma values of histamine, but low plasma histamine was linked to a severe reaction during inhalation of the antigen.[14]

A dose of 300 mg/day of freeze-dried Urtica dioica is recommended for the treatment of allergic rhinitis.[11] Side effects are rare, typically allergic and gastric in nature, the latter due to ingesting the medication on an empty stomach.

Bromelain

Bromelain, a glycoprotein with one oligosaccharide moiety and one reactive sulfhydryl group for each molecule, is a proteolytic enzyme derived from the stem of the pineapple plant (Ananas comosus). The optimal activity of this enzyme is between pH 5.0 and 8.0. Bromelain has been found to be an effective mucolytic agent in respiratory tract diseases.[15] Bromelain's pharmacological activity is via several mechanisms (Table 1).

Table 1: Bromelain: Mechanisms of Action.

* Induction of proteolytic activity at **inflammatory** sites

* Activation of fibrinolysis activity via the plasminogen-plasmin system

* Depletion of kininogen

* Inhibition of pro-**inflammatory** prostaglandin biosynthesis and initiation of prostaglandin E1 accumulation (which inhibits the release of polymorphonuclear leukocyte lysosomal enzymes).[16-18]

Tissue damage stimulates the kinin, complement, fibrinolytic, and clotting systems. The role of fibrin in the promotion of the **inflammatory** response is to form a matrix that sequesters the area of inflammation, resulting in nutritive circulatory repression, inadequate tissue drainage, and subsequent edema. The kinin system cascade concomitantly generates kinins (e.g., bradykinin and kallidin) which function to increase vascular permeability; this produces edema and pain. Bromelain counteracts the fibrin and kinin pathways by stimulating plasmin production. This results in depolymerization of fibrin, thereby preventing fibrin-clogged venous stasis and localized edema.[16,17]

Plasmin has been shown to block the mobilization of endogenous arachidonic acid by phospholipases, thereby reducing platelet aggregation and possibly other prostaglandin-mediated phenomena.[19] Bromelain has also been shown to reduce plasma kininogen, resulting in inhibition in the production of kinins. The depletion of kininogen and the activation of plasmin are essentially the pharmacological effects thought to reduce the edema and inflammation associated with allergic rhinitis.[17,19]

The therapeutic dose for allergic rhinitis ranges from 400-500 mg

three times daily of an 1800-2000 m.c.u. potency bromelain.[19] Some authorities believe that, due to bromelain's documented effect as a digestive enzyme post-pancreatectomy, healing adjunct for gastric ulcers, and prophylactic agent for enterotoxin-induced diarrhea, bromelain should be taken on an empty stomach.[19] However, existing literature does not compare the efficacy of bromelain when administered either with or between meals. Bromelain demonstrates very low toxicity with an [LD.sub.50] greater than 10 g/kg.[19] Allergic reactions may occur in those who are sensitive to pineapple. Nausea, vomiting, diarrhea, menorrhagia, and metrorrhagia are unlikely side effects.

Quercetin

Quercetin is a **flavonoid** aglycone of rutin and is found in a wide variety of vegetables and herbs. Quercetin inhibits **inflammatory** processes attributed to activated neutrophils due to membrane stabilization, potent antioxidant effects and inhibition of the enzyme hyaluronidase (which prevents the breakdown of collagen matrix). Membrane stabilization results in prevention of mast cell and basophil degranulation and decreased inflammation by inhibition of neutrophil lysosomal enzyme secretion and leukotriene production.[20,21]

In a Japanese study of mast cells from nasal mucosa of individuals with perennial allergic rhinitis, quercetin significantly inhibited antigen-stimulated histamine release. Quercetin's effect was almost twice that of sodium cromoglycate at the same concentration.[22]

The recommended dosage for allergic rhinitis ranges from 250-600 mg, three times daily, five to ten minutes before meals.[23,24] Quercetin's efficacy may be enhanced when bromelain is taken concomitantly.[17]

N-Acetylcysteine

N-acetylcysteine (NAC) is a natural, sulfur-containing amino acid derivative that detoxifies as well as protects cells and cellular components against oxidative stress. NAC has been documented as an effective mucolytic agent in individuals with chronic bronchitis, cystic fibrosis, asthma, sinusitis, and pneumonia. A dosage of 200 mg twice daily was found to decrease symptoms of chronic bronchitis.[25] NAC helps reduce the viscosity of mucus so it may be more easily expectorated,[26] accomplishing this by converting the disulfide bonds of the mucoproteins into sulfhydryl bonds and cleaving the mucoproteins into smaller molecules.

While specific research on the use of NAC for allergic rhinitis has not been conducted, because of its affinity for mucus membranes, both as an antioxidant and mucolytic, it may have application as part of a treatment protocol for allergic rhinitis. Recommended therapeutic dosages range from 500 mg to 2 gm daily.

Vitamin C

Vitamin C has been found to exert a number of effects on

histamine. It appears to prevent the secretion of histamine by white blood cells and increase its detoxification.[27] Histamine levels were found to increase exponentially as ascorbic acid levels in the plasma decreased.[28]

In a study of the effectiveness of intranasal vitamin C, 48 subjects received either ascorbic acid solution (n=27) or placebo (n=21) sprayed into the nose three times daily. After two weeks 74 percent of subjects treated with ascorbate solution were found to have decreased nasal secretions, blockage, and edema. Improvement was seen in only 24 percent of placebo treated patients. The pH of the secretions in the allergic rhinitis sufferers appeared to be more alkaline, over 7.0, with normal nasal secretions tending be in the range of 5.5-7.0. The pH of nasal secretion was' found to be within normal ranges after administration of vitamin C; patients with nasal pH's closer to 8.0 seemed to respond more favorably to the vitamin C therapy.[29]

Vitamin C is nontoxic and virtually free of side effects, diarrhea and abdominal distention being the most common. For allergic rhinitis, a dosage of at least 2 grams per day should be administered.[30]

Summary

Evaluation of current therapeutic strategies for the management of allergic rhinitis revealed that only 26 percent of the reported population suffering from allergic rhinitis believed their symptoms were "well-controlled" or "completely controlled;" while 52 percent believed effective treatments were available.[31] Health-care practitioners can utilize a combination of botanical medicines and nutrients based on the diagnostic impression developed via physical examination, patient history, and other diagnostic measures. Urtica dioica, bromelain, quercetin, and vitamin C have relatively well-documented individual outcomes on their efficacy in treating allergic conditions; NAC has some well-documented benefit for various respiratory disorders. The combination of all of them as part of a therapeutic treatment plan has yet to be validated. Other supplements that may be useful for the treatment of allergic rhinitis, but not reviewed in this paper, include chamomile, elder flower, eyebright, garlic, goldenrod, feverfew, yarrow, vitamins A, B, and E, selenium, royal jelly, ephedra, hydrangea root, Ligusticum porteri, and olive leaf.

[Figure 2 ILLUSTRATION OMITTED]

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Allergies

Overview

About 7% of all Americans suffer from hay fever, an allergic condition that can cause runny nose, sneezing, and teary eyes. It is known officially as *allergic rhinitis, allergic sinusitis,* or *allergic conjunctivitis,* depending on whether symptoms manifest mainly in the nose, sinuses, or eyes, respectively. Hay fever usually peaks when particular plants are pollinating or when molds are flourishing. People who suffer from year-round hay fever may be allergic to ever-present allergens such as dust mites.

Here's how hay fever works. In response to the triggers noted above, an individual prone to allergies develops an exaggerated immune response. Substances known as IgEs flood the nasal passages, white blood cells called eosinophils arrive by the millions and billions, and **inflammatory substances such as histamine, prostaglandins, and leukotrienes are released in massive amounts. The overall effect is the familiar one of swelling, dripping, itching, and aching.**

The mechanism of allergic response is fairly well understood. Why allergic people react so excessively to innocent bits of pollen, however, remains a complete mystery.

Conventional treatment for hay fever consists of antihistamines (now available in forms that don't make you sleepy); decongestants, nasal steroids, or cromolyn sodium; and occasionally allergic desensitization ("allergy shots"). For most people, some combination of these

Library (1 - 8 of 8)

- Study Shows Simple Steps Can Reduce Dust Mite Allergens in Bedrooms
- Dietary Fatty Acids May Influence the Development of Childhood Allergic Diseases
- Allergy Drugs Likely Face Court Battle
- FDA May Change Drug Status
- Avoiding Spring Allergies: An Outdoor Checklist
- Keep Allergies at Bay: Tips for Prevention and Treatment
- Sweep Allergies From Your Home: A Room-by-Room Checklist
- Allergy Shots Keep Hitting Hay Fever for Years After Treatment Ends

treatments will be successful.

Natural Treatments for Allergies

The following treatments are widely recommended for allergies, but they have not been scientifically proven effective at this time.

Nettle Leaf

According to one preliminary double-blind placebo-controlled study, freeze-dried extract of stinging nettle leaf can at least slightly improve allergy symptoms.[1]

A typical dosage is two to three 300 mg capsules of nettle leaf. Nettle leaf has an extensive history of use in food and is believed to be safe. However, safety in young children, pregnant or nursing women, and those with severe liver or kidney disease has not been established.

For theoretical reasons, some researchers suggest that nettle may interact with conventional medications for diabetes and high blood pressure, but no actual problems of this type have been officially reported.

Quercetin, OPCs, and Other Flavonoids

Test-tube studies suggest that flavonoids—biologically active compounds found in many plants—may help reduce allergy symptoms.[2–5] A particular flavonoid, quercetin, seems to be one of the most active.[6–10] Many texts on natural medicine claim that quercetin works like the drug cromolyn (Intal) by stopping the release of allergenic substances in the body. However, while we have direct evidence that cromolyn is effective, there have not been any published studies in which people were given quercetin and their allergic symptoms decreased. It is a long way from test-tube studies to real people. If you do wish to take quercetin, a particular form of the substance, *quercetin chalcone*, may be better absorbed than other forms.

OPCs from grape seed or pine bark are also often said to be effective. But at the present time, we don't really know whether any of these treatments are really helpful for allergies.

Vitamin C

Vitamin C is often suggested as a treatment for allergies, but the research results are very preliminary and somewhat contradictory.[11,12,13]

Other Treatments

Vitamin B6, vitamin B12, cat's claw, *Coleus forskohlii*, GLA, fish oil, and betaine hydrochloride are sometimes recommended for hay fever, but there is as yet no significant evidence that they are effective.

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NSAID Duplicate Therapy

Why a non-selective NSAID and a selective COX-2 inhibitor should not be used concomitantly

Months Reviewed: June, July and August 2000
Intervention Mailed: October 2000

FINAL REPORT

Background/Rationale

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat pain and inflammation associated with various disorders. The effects of NSAIDs are due to the inhibition of the enzyme cyclooxygenase. The two identified forms of this enzyme are cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Non-selective NSAIDs (e.g., ibuprofen, naproxen) inhibit both COX-1 and COX-2 enzymes, while COX-2 selective NSAIDs (e.g., celecoxib and rofecoxib) only inhibit the COX-2 enzyme. Meloxicam is a selective, but not specific COX-2 **inhibitor**, which may affect COX-1 at higher therapeutic doses. [8]

COX-1 is responsible for the production of protective prostaglandins (PGs). Not only do PGs help maintain the integrity of the gastric mucosa, they also mediate normal platelet function and regulate renal blood flow. Specifically, PG has been found to inhibit gastric acid secretion, assist in mucus secretion and bicarbonate ion secretion, and to have an effect on mucosal blood flow. COX-2 is an inducible enzyme which is responsible for the production of PGs associated with pain and inflammation.

Inhibition of COX-2 provides relief of pain and inflammation. The inhibition of COX-1 leaves the gastric mucosa susceptible to damage and the formation of gastric ulcers which may result in perforations, bleeding, or obstruction. Therefore, patients treated with non-selective NSAIDs may experience GI complications. Patients at high-risk for gastrointestinal complications secondary to non-selective NSAIDs are listed in Table 1. [1]

The therapeutic efficacy of the COX-2 selective NSAIDs is comparable to the non-selective NSAIDs. In general, the COX-2 selective NSAIDs are well tolerated. [2-6] The incidence of headache, abdominal pain, diarrhea, and dyspepsia associated with the new COX-2 selective NSAIDs are similar to the non-selective NSAIDs. [2-6] (See Table 2 & 3) The incidence of serious GI complications is slightly lower with selective COX-2 inhibitors versus non-selective NSAIDs. The overall relative risk for development of a confirmed gastric ulceration (by endoscopy) for rofecoxib vs. NSAIDs is 0.51. [5] COX-2 inhibitors have not been shown to be renal protective and do not inhibit platelet activation.

Considering there is no difference in efficacy, a disadvantage to prescribing a COX-2 **inhibitor** is the higher cost of the drug compared to a non-selective NSAID. Currently, the average wholesale price for a thirty day supply of celecoxib 200 mg or rofecoxib 25 mg is $73, while the same supply of naproxen 500 mg is $59 and ibuprofen 800 mg is $33. (See Table 4) Based on a number-needed-to treat analysis, it has been suggested that prevention of adverse effects may justify prescribing COX-2 agents to high-risk patients, such as those 75 years or older with a prior history of ulcer or gastrointestinal tract bleeding. [7] While cost favors the use of generic, non-selective NSAIDs, the decision to use the more expensive COX-2 inhibitors should be based on the patient's risk of gastrointestinal tract hemorrhage. [8]

At this time, no clinical trial has shown increased efficacy with the concomitant use of a non-selective NSAID with a new COX-2 inhibitor. The selectivity of the COX-2 inhibitor will be lost with the addition of the non-selective NSAID that inhibits both COX-1 and COX-2. Therefore, the benefit of possible reduced incidence in gastric ulcer formation will be negated when duplicate therapy is initiated and the cost of drug therapy will increase. It is in the patients' best interest to only receive one NSAID at a time. Given the high cost of the COX-2 selective NSAIDs, proper prescribing will be important in the future. Additionally, increased efficacy has not been shown with concomitant use of two non-selective NSAIDs or two selective COX-2 inhibitor NSAIDs. It is important to maximize the dose of a single NSAID before considering alternative therapy. At this time concomitant NSAID therapy does not improve efficacy, may increase incidence of GI complications, and increases drug therapy costs.

Table 1: Risk factors for NSAID-induced upper gastrointestinal complications

History of peptic ulcer disease/ upper gastrointestinal bleed or perforation
Concomitant corticosteroid therapy
High dose and multiple NSAID use
Anticoagulant treatment or coagulopathy
Patients > 60 years
Smoking or alcohol abuse

Table 2: Percent Adverse Events

Adverse event	Rofecoxib 25 mg qd [5]	Ibuprofen 800 mg tid [5]
Diarrhea	5	5
Dyspepsia	24	26
Epigastric discomfort	6	8
Nausea	7	4

Table 3: Percent Adverse Events

Adverse event	Celecoxib 100 mg bid	Naproxen 500 mg bid
Headache	18,[2] 16[3]	14,[2] 16[3]
Abdominal pain	4[2,3]	6,[2] 7[3]
Diarrhea	5[2,3]	6,[2] 4[3]
Dyspepsia	10[2,3]	12[2,3]

Table 4: Current NSAID Costs

Medication	Dose	AWP *	NM Medicaid ReimbursementCosts*

Celecoxib	200 mg qd	$73	$68
Rofecoxib	25 mg qd	$73	$70
Naproxen	500 mg bid	$59	$15
Ibuprofen	800 mg tid	$33	$14

**Costs are based on a 30-day supply necessary to treat osteoarthritis*

Goal

To reduce the prescribing of NSAIDs concomitantly by educating prescribers and pharmacists.

Hypothesis

NSAIDs are being prescribed concomitantly

Methods

A literature search was undertaken to identify studies on efficacy and safety of the use of new COX-2 inhibitors. The following databases were searched: Medline 1997-2000, IPA, and SciSearch. Prescription claims for NM Medicaid patients receiving two NSAIDs were reviewed.

A. Inclusion Criteria

1. Identify and include New Mexico Medicaid fee-for-service patients who have received duplicate nonsteroidal anti-inflammatory drug (NSAID) therapy during June, July and August 2000.

2. NSAID therapy is defined according to the AHFS classification 28:08.04.

Non-selective NSAIDs	Non-selective NSAIDs cont.	Selective COX-2 inhibitors
Diclofenac	Meloxicam	Celecoxib
Diflunisal	Nabumetone	Rofecoxib
Etodolac	Naproxen/Naproxen Na	
Fenoprofen	Oxaprozin	
Ibuprofen	Piroxicam	
Indomethacin	Salicylate salts	
Ketoprofen	Salsalate	
Ketorolac	Sulindac	
Meclofenamate	Tolmetin	
Mefenamic acid		

Aspirin, AHFS classification 28:08.04, will be excluded.

Aspirin was excluded from the list of NSAIDs for the following reasons. Low dose **aspirin** therapy is recommended for primary prevention of cardiovascular disease in high-risk men and women with Type 1 or 2 diabetes, and for secondary prevention of cardiovascular disease in diabetic men and women who have evidence of large vessel disease. [9] **Aspirin** may also be prescribed to minimize symptoms of angina, as an alternative to warfarin in patients with a previous history of nonvalvular atrial fibrillation, and for the reduction of risk for stroke in patients with transient ischemic attacks or minor stroke. [10] Due to the limitations of the database, it is difficult to identify patients with these disease states. In addition, COX-2 selective inhibitors are not a substitute for **aspirin** for cardiovascular protection, and they can be used with low-dose **aspirin** therapy. However, concomitant use of a COX-2 **inhibitor** and **aspirin** may increase the risk of gastrointestinal adverse events, because **aspirin** dosages as low as 10mg are capable of suppressing prostaglandin synthesis in the gastric mucosa..

3. Duplicate therapy is defined as a prescription claim for: two non-selective NSAIDs, two COX-2 inhibitors, or a non-selective NSAID and a COX-2 **inhibitor** for a total of a 50 day supply or greater of each drug over the three month period.

B. Exclusion Criteria

1. Patients where the last NSAID prescription claim date is before the first COX-2 inhibitor prescription claim date or vice-versa.
2. Patients where the last prescription claims date for the 1st COX-2 inhibitor is before the first prescription claim date for the 2nd COX-2 inhibitor or vice-versa.
3. Patients where the last prescription claims date for the 1st NSAID is before the first prescription claim date for the 2nd NSAID or vice-versa.
4. Patients who did not receive any NSAID or COX-2 prescriptions in August 2000.

C. Educational material and response forms and prescription profiles will be mailed to prescribers and pharmacists for the above identified patients.

D. Reports will be submitted to the DUR board.

E. Outcome analyses will be performed three months following the mailing of the intervention packet. The analyses will include: a review of prescription claims to determine if prescribing changes have occurred, a cost analysis, and a review of outpatient and hospital claims to identify GI complications.

Table 5: Inclusion and Exclusion Criteria

Inclusion Criteria	Total
Total prescription claims for non-selective NSAIDs and COX-2s (6/00-8/00).	12,381
Total patients on non-selective NSAID and/or COX-2 therapy (6/00-8/00)	6638
Inclusion Criteria (non-selective NSAID + COX-2)	
Total patients with NSAID and COX-2 therapy (6/00-8/00).	341 *
Exclusion Criteria (non-selective NSAID + COX-2)	
Total patients excluded with last NSAID prescription before first COX-2 or vice versa (patients switching therapy).	221
Total patients excluded with days supply less than 50 for either NSAID or COX-2.	90
Excluded due to no Rx in August.	0
Total patients receiving duplicate NSAID + COX2 that met criteria	30

Inclusion Criteria (COX-2 + COX-2)	
Total patients with COX-2 therapy (6/00-8/00)	1917
Total patients with two COX-2 prescriptions.	67*
Exclusion Criteria (COX-2 + COX-2)	
Total patients excluded with days supply less than 50 for either COX-2.	51
Total patients excluded with last prescription of 1st COX-2 before first prescription of 2nd COX-2 or vice versa (patients switching therapy).	4
Excluded due to no Rx in August.	0
Total patients with COX-2 days supply greater than or equal to 50 and not switching therapy.	12
Inclusion Criteria (non-selective NSAID + non-selective NSAID)	
Total patients with NSAID therapy (6/00-8/00)	4380
Total patients with two NSAID prescriptions 6/00-8/00.	283
Exclusion Criteria (non-selective NSAID + non-selective NSAID)	
Total patients excluded with days supply less than 50 for either NSAID.	258
Total Patients excluded with last prescription of 1st NSAID before first prescription of 2nd NSAID (patients switching therapy).	4
Excluded due to no Rx in August.	5
Excluded patients that did not meet inclusion criteria after phone calls and clinical pharmacist review.	2
Total NSAID+NSAID patients.	14
Total patients used for intervention.	55

* Patient case number 53 appeared in both the NSAID+COX-2 table and the COX-2+COX-2 table. Patient was receiving two COX-2s and one NSAID and was included only once in the final intervention.

Two patients were receiving Acular eye drops as their duplicate NSAID therapy and the patients were excluded.

Table 6: Telephone Call and Intervention Mailing Information

Telephone Call Information	Total	
Number of Prescriptions missing Prescriber information.	96/321	30%
Number of Prescriptions in which the Prescriber remains unidentified	0	

Intervention Mailing	Total
Patients included in the Intervention	55
Prescribers Identified	74
Total Prescriber Response forms mailed (for each patient per prescriber)	80
Pharmacies Identified	50
Total Pharmacy Response forms mailed (for each patient per pharmacy)	61
Consultant Pharmacists Identified	3
Total Consultant Pharmacist Response forms mailed (for each patient per pharmacist)	4
Packets mailed	127
Response forms mailed	145
Intervention Mail Date	10/10/2000
Requested Return Date	11/10/2000

Table 7: Intervention Responses as of 11/21/00

Intervention Responses as of 11/21/00	Number	%
Prescriber packets resent with new addresses	5/74	6.8%
Undeliverable prescriber packets	1/74	1.4%
Prescribers Responding	27/73	37%
Prescriber Response Forms Received	27/79	34%
Pharmacies Responding	21/50	42%
Pharmacy Response Forms Received	25/61	41%
Consultant Pharmacists Responding	1/3	33%
Consultant Pharmacist Response Forms Received	1/4	25%
Response Form Returned On Behalf of Patient (at least one form returned per patient)	**36/55**	**65.5%**

Results

NSAID = non-selective
COX-2 = selective

Table 8: Prescriber Responses

Prescriber response forms returned: 27/79 (34%)

Prescribers responding they would consider changes: 10/27 (37%)	6/10	(60%)	Discontinued NSAID
	1/10	(10%)	Discontinued both NSAIDs
	2/10	(20%)	Discontinued COX-2 **inhibitor**
	1/10	(10%)	Discontinued both COX-2 inhibitors
Prescribers responding they would not consider change: 17/27 (63%)	2/17	(12%)	Never seen this patient
	5/17	(29%)	No longer a patient of prescriber
	3/17	(18%)	Patient is deceased
	3/17	(18%)	Patient alternates medications and wants to continue
	1/17	(6%)	current therapy
			My prescription was appropriate. Only prescribed one

1/17	(6%)	of the meds Narcotics not an option
1/17	(6%)	High risk gastric ulcer
1/17	(6%)	No reason given

Additional prescribers comments : Patient noncompliance and prescribing by multiple providers are most frequently sited as reasons for duplicate therapy.

Estimated average time to complete survey: 5.6 minutes

Table 9: Pharmacy Responses

Pharmacy response forms returned: 25/61 (41%)

Pharmacists responding they planned to take action:	9/24	(38%)	Pharmacists who called the prescriber
	4/24	(17%)	3/9 (33%) Discontinued COX-2 **inhibitor** 2/9 (22%) Discontinued NSAID
24/25			4/9 (44%) No change in both NSAID and COX-2 **inhibitor**
			1/4 No response from prescriber
(96%)			2/4 Patient is stable on current medications
			1/4 Patient to discontinue ineffective med
			Pharmacists who called the patient and will speak with the
			patient at the time of next refill
	2/24	5/24 (21%)	2/4 (50%) Discontinued one of the NSAIDs and one of the COX-2 inhibitors
			1/4 (25%) Discontinued both NSAIDs
			1/4 (25%) Discontinued one of the NSAIDs
			Pharmacists who called the prescriber and called the patient and will speak with the patient at the time of next refill
			2/2 (100%) Prescriber has not yet responded
			Pharmacists who will speak with the patient at the time of next
			refill
			1/5 (20%) Patient alternates medication
			1/5 (20%) Discontinued NSAID
			1/5 (20%) Discontinued COX-2
			1/5 (20%) **Combination** works for the patient
			1/5 (20%) Is M.D.'s business
			Pharmacists who called the patient.
			1/1 (100%) Discontinued NSAID
			Pharmacists who did not indicate responses but had actions
			2/3 (67%) Discontinued COX-2
			1/3 (33%) Determining which medication works better

Pharmacists responding they planned to take no action: 1/25 (4%)	1/1	(100%)	Patient is no longer receiving medications there.

Estimated average time to complete survey: 10 minutes

Table 10: Consultant Pharmacist Responses

Consultant pharmacist response forms returned: 1/4 (25%)

Consultant pharmacists responding they planned to take action: 1/1 (100%)	1/1 (100%)	Discontinued both medications (both were COX-2 inhibitors)

Discussion

The prescriber, pharmacist and consultant pharmacist response rates were 37%, 42%, and 33% respectively. The slightly lower response rate for pharmacies may be a result of the additional time it takes to contact the prescriber, review the patient's medication record or contact and discuss care with the patient.

Of the responding prescribers, thirty-seven percent responded that they would consider changes in their patient's medical regimen. Of those considering changes, sixty percent discontinued one of the non-selective NSAIDs, ten percent discontinued both non-selective NSAIDs, twenty percent discontinued one of the selective COX-2 inhibitors, and ten percent discontinued both COX-2 inhibitors. Sixty-three percent of the responding prescribers indicated that they planned to take no action. The majority of these prescribers (29%) responded that they were no longer seeing the patient and twelve percent had never seen the patient. Eighteen percent stated that the patient was deceased and another eighteen percent were honoring requests from the patient to remain on their current therapy. The remaining twenty-four percent gave other reasons for not taking action such as; narcotics not an option, high risk gastric ulcer, unaware of patient seeing other providers and obtaining other prescriptions.

Of the responding pharmacies, ninety-six percent responded that they planned to take action. Thirty-eight percent of the pharmacists called the prescriber with thirty-three percent discontinuing the selective COX-2 inhibitor and twenty-two percent discontinuing the non-selective NSAID. The remaining forty-four percent did not change the drug regimen because the prescriber didn't respond, the patient requested to remain on current medications, or the patient was to discontinue the ineffective medication. Only one pharmacist responded that no action would be taken because the patient no longer received their medications at that pharmacy.

The consultant pharmacists response rate was low (33%) for unknown reason. Of the one responding pharmacist, action was taken and both selective COX-2 inhibitors were discontinued.

Conclusion

This intervention has provided an opportunity to educate prescribers and pharmacists regarding concomitant NSAID therapy. As a result of this information, some changes in therapy are planned. Most of the prescribers discontinued the non-selective NSAID and the pharmacies tended to discontinue either the selective COX-2 or the non-selective NSAID. The pharmacy response rate may be low due to the time requirement. The consultant pharmacist response was also low. The reason for this low response rate is unclear.

Follow-up

The June, July, and August 2000 prescription claims for the patients included in this intervention will be reviewed to determine if actual changes have been made in NSAID therapy. In addition, an economic analysis will be performed. Our program continues to strive to obtain accurate address of the prescribers and patient information in order to improve the efficacy of our interventions.

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Behind the Cancer Headlines

May 1, 2001

Keep an Eye on Cox-2 Inhibitors

In a presentation at the recent Science Writers Seminar sponsored by the American Cancer Society, Dr. Ernest Hawk of the National Cancer Institute reported on a new class of drugs called Cox-2 inhibitors that appear to have extraordinary potential for treating a wide range of cancers.

This is remarkable because Cox-2 (cyclooxygenase-2) inhibitors are basically aspirin derivates that were originally developed to ease pain in patients with chronic diseases such as arthritis.

A New Class of Cancer Drugs

For years, researchers have suspected that certain ingredients in aspirin might inhibit an enzyme called cyclooxygenase (COX), which has been associated with an increased risk of colorectal cancer. But they were hesitant to recommend aspirin to these patients because long-term aspirin use could result in stomach ulcers and intestinal bleeding.

However, scientists soon learned that there are actually two forms of the COX enzyme-COX-1, which is necessary to maintain overall health; and COX-2, which is linked to inflammation and tumor formation. Cancer researchers began searching for ways to "inhibit" COX-2 as a potential new treatment for colorectal cancer.

A landmark National Institute of Cancer study was then undertaken to see if a new COX-2 inhibitor, celecoxib, could reduce the number of precancerous polyps

occurring the people with an inherited predisposition to colon cancer. In fact, the number of polyps was reduced by 28 percent in those patients taking celecoxib.

Treating Many Cancers

The success of that NCI study prompted a number of similar investigations to see if COX-2 inhibitors might have a similar impact on preventing-and treating-other cancers.

At the American Cancer Society seminar, Hawk noted that more than a half-dozen COX-2 inhibitors are currently being researched to treat a variety of cancers. He specifically pointed out studies that have linked COX-2 inhibitors with reductions in breast, prostate, head and neck, bladder, colon and pancreatic cancers.

Hawk further emphasized that COX-2 inhibitors may have a wide-ranging benefit throughout the cancer development process, from pre-invasive lesions to metastatic disease. In fact, The National Institute of Cancer is also expanding its initial research with celecoxib to see if it can thwart colon cancer at various stages of its development.

Much to Learn

Researchers still don't know exactly how COX-2 inhibitors act to prevent cancer. But they do know that COX-2 inhibitors reduce the production of free radicals, which are involved in the uncontrolled cellular growth that is a characteristic of cancer.

There are some extremely promising clinical trials now underway which should help answer these and other questions about the mechanism of COX-2 inhibitors-and their extraordinary potential for treating a wide range of cancers. Stay tuned.

SOURCES:

American Cancer Society Science Writers Seminar, April 24, 2001, Dana Point, California
The National Cancer Institute (http://www.nci.nih.gov)
The American Cancer Society (http://www2.cancer.org)

REPORT FROM THE 1999 MEETING

An Internet friend, MH sent me her notes from the September 1999 Cancer Control Society Conference on Alternative treatments.

This organization has an annual meeting where speakers talk about some of the clinics and hospitals offering "alternative" therapies. They also run a clinic tour where people are driven from one clinic to another, meet patients and view the facilities. Here are some excerpts:

Dr. Aristo Vojdani, MD suggested that two major causes of cancer are smoking and diet. He stressed the use of antioxidants-Vit. C, E. selenium and Vit. A/carotenes, suggesting that they could improve natural killer (NK) cells. Much of his presentation was focused on dietary changes and the results achievable. Contact him at (310) 657-1077 in Beverly Hills, CA. www.immuno-sci-lab.com

Dr. Michael Bennett of the University of CA, SF Pharm talked about flaxseeds suggesting that the golden seeds were of greater value than the brown ones. ¼ cup per day contains enough lignans needed for cardiovascular problems as well as prevention/treatment of breast cancer. He said it might also help with hot flashes. You need to grind the seeds until fine before using- you can safely grind a 5-day supply if it is stored in the refrigerator. He mentioned a company that offered gold flaxseeds-Heintzman Farms, (877) 439-7611 or www.flaxgold.com

Dr. Samuel Epstein spoke about the cancer epidemic. He is the author of several books including "The Politics of Cancer". He suggested that water, consumer products, the workplace and other environmental issues contribute enormously to the problems. He mentioned studies that demonstrate that aspirin acts as a **COX2 inhibitor** and can reduce breast cancer risk if taken 3 times a day for five years. (1966 study showed 30% reduction).

He also argued against pre-menopausal mammography, since it is not very valid due to dense breast tissue, and exposes women to ionizing radiation unnecessarily. He also suggests avoiding or reducing use of alcohol, giving up smoking, not using dark hair dyes and emphasized exercise. He spoke against using long-term oral contraceptives, use of hormone replacement therapy, use of anti-hypertensives, silicone-gel breast implants, diet high in animal fats and dairy products containing rBGH (bovine growth hormone), and warned of the dangers of household chemicals.

Ann's NOTE: See the section under environment that offers alternatives to commercial cleaning products.

Peter Chowka, a journalist spoke about the powerful, anecdotal evidence of the efficacy of the Hoxsey formula and Centro BioMedico (a treatment center). He mentioned that the University of Texas/Alt Med Ctr. offers information on this.

Ann's NOTE: see the section for this under links. It is possible to go to the Centro BioMedico as an outpatient, cost of treatment is $3500 for life but there are additional costs for special treatments. Peter Chowka writes for http://naturalhealthline.com/

Hospital Santa Monica-Dr. Kurt Donsbach discussed the therapies offered at his clinic which includes cartilage, oxygen therapy, Rife, IP6, Resveratrol (grape seed extract anti-oxidant), Arginine, Curcumin, NTO and lactoferrin. He told the audience that arginine inhibits tumor growth and can prevent liver/kidney metastasis. Curcumin is good for colon cancer and is an **inhibitor** of tumor promotion, reducing incidence of adenomas (non-malignant tumors). Lactoferrin is said to reduce free iron in the blood and prevent metastases, good for pancreatic cancer and leukemia.

NTO can fill a growth receptor site on a cancer cell, but it must be taken for life. He also mentioned CoQq10, Lycopene, Genistein, Vitamin D, Retinoic Acid (a form of Vitamin A), Melatonin, DHEA, Green Tea extract, Germanium, hyperthermia, UV irradiation of the blood, bio-magnets and oxygen therapy.

Ann's NOTE: The cost of these treatment may add up to quite a lot of money and is probably not reimbursable. Many of the things he mentions ARE known to be cancer fighters. Donsbach tends to talk in terms of cure. Nowadays we consider that cancer can be

treated as a chronic disease but needs constant attention.
http://www.hospitalsantamonica.com/index.htm

American Metabolic Institute-Dr. Geronimo Rubio told the audience that they offer the Rife frequency generator, sometimes in conjunction with low dose radiation (1/10 of the usual amount). They have used chemotherapy as well. A poultice of green cabbage leaves can remove radiation toxins. He said that a bath of sea salt or sodium bicarbonate, ginger and IV EDTA (chelation) would help rid the body of toxins from chemotherapy. They also use an autologous vaccine therapy (from patient's own blood, urine or tumor tissue) given intravenously for five years or more. Enzymes are also used. There is a strong focus on diet, both macrobiotic and blood type. Coffee enemas and colonics are given. Colostrum is used to protect the intestines. They also use herbs such as Cat's Claw, Essiac. Cuachalate tea (check out www.herbsofMexico.com), a hormone blocker and Pau D'Arco.

There are other therapies offered at this clinic as well including lipids, oxygen, Laetrile, shark cartilage, peptides and Clodronate (a treatment for bone mets) with Poly-MVA. They teach patients to use visualization, believe in ultrasounds and do both a DNA and the AMAS test.

Ann's NOTE: AMAS is a blood test that is said to be predictive of cancer up to 18 months. Blood is sent to Boston for this test. Patient or doctor has to call for a special kit. See Ann's Bio for some of my take on this.

Daniel Nadeau (dnadeau@emh.org) spoke about the importance of intestinal health for overall well being. Nutraflora FOS, a substrate for bifidobacteria, can lower cholesterol and prevent tumors. He said that short-chained FOS can improve mineral and bone absorption.

An enema with scFOX can be particularly helpful in reducing inflammation, but suggested that fiber is better than relying on enemas. FOS is in many Japanese foods. It is beneficial for osteoporosis, liver and renal disease, and useful after chemotherapy and radiation. He said that the product Ensure with FOS is useful and is sold as a supplement at health food stores.

Elaine Teune, a resource person, spoke about a Rife machine she considers superior to most on the market today. It is called Biotec 2000. She mentioned a metabolic testing kit that sells for $79.95 and helps you determine what

supplements you need. She said that Douglas Labs (of MetaMetrix Labs) will compound supplements in pills.

Frank Schallenberger, MD of Carson City, NV has been working with ozone therapy for twenty years. He said it was inexpensive, but should not be used as a primary cancer therapy. He suggested it would be helpful before and after chemotherapy since it can increase tissue oxidation, and is alkalizing. He said it was helpful for lung, vaginal, rectal and bladder cancer. He also works by injecting ozone into parts of the body.

This is called Major Auto Hemotherapy (MAH). It is intra-muscular (IM), re-infused blood into the body or by intravenous ozonated saline. This therapy was said to help people with diabetes, hepatitis, chronic fibromyalgia, acute infections, autoimmune diseases, cardiovascular, osteoarthritis, chronic pain syndromes and gangrene. www.antiagingmedicine.com (570) 524-5004

Hal Huggins, DDS of Colorado Springs, CO is well known for his championship of removing mercury fillings. He had or has a laboratory that used blood samples to tell patients what materials to avoid when having cavities filled. He said to avoid gold and nickel crowns. Also not to use copper in the mouth. He referred the audience to Dr. Morales of Puerto Vallarta for a removal program at a cost of $3000.

Dr. Douglas Brody of Reno, NV spoke about compassionate care. He discussed his protocol which consists of infusions: sterile water, Potassium chloride, Magnesium sulfate, Selenium, Manganese, Glutathione, Germanium, Zinc, Chromium, Molybdenum, Folic Acid, B complex, Pyridoxine, Ascorbic Acid, Calcium, Gluconate and Cyanosoblamin (??). He adds DMSO for brain and leukemia patients. He also gives super C infusions consisting of dextrose and beet-derived C, Calcium gluconate, Magnesium sulfate, Potassium chloride, Sodium bicarbonate. He also gives insulin prior to these Super C infusions. Insulin apparently acts to enhance the activity and transport of the infusion. Higher blood sugar will nullify those effects. Cancer cells like glucose and do not like potassium.

For oral supplements, he recommends: Multivitamin B complex, glutathione, selenium, Vitamin C (6,000-12,000 mgs) in divided dosage, Beta 1, 3 glucan (one cap twice a day), IP6 (2 caps 3 times daily before meals), Amygdalin (500mgs 3 times daily with meals-this is also known as Laetrile), hydrazine sulfate Ann's NOTE: Please see the

section on hydrazine sulfate under Consumer's View of Alt Med for the many foods to avoid when using hydrazine sulfate), pycnogenol, thymus, CoQ10, and Vitamin E.

For lymphoma patients he adds Butyrate (Butyrex) 2 caps three times with meals. For melanoma he adds azelaic acid (1.5 mg four times a day with meals), interferon injection, Butyrate and L-Carnitine (one cap three times a day). Azelaic acid is non-toxic, being studied in Italy and works by inhibiting tyrosine; it is used in conjunction with L-Carnitine. Glutathione restores liver function, which enhances detox and the immune system.

Dan Rogers, MD, ISSELS/CHIPSA (Gerson Research Organization) reported using urea/creatine by injection directly into the tumor site. They are also using a hyperbaric chamber. For Hodgkin's and thyroid patients, they are using the Issels vaccine therapy as well as Govallo VG 1000 as a vaccine. Coley's toxins are given to speed up a fever reaction. Other protocol substances include high Potassium, cod liver oil, raw fruits and vegetables, enzymes and chelation. Dr. Rogers stated that they are having good success in reducing tumors in melanoma, breast, astrocytoma and lymphoma patients, claiming a 28% overall patient survival rate which includes many Stage3 and 4 patients. http://www.issels.com .

Ann's NOTE: See the section labeled Gerson Clinic/Mexico in which I describe my 1996 stay at this clinic, there is also a link to it.

Stanley Jacob of Health Sciences University, Portland, OR. is known as the "father of DMSO". He was given the Humanitarian award by the Cancer Control Society. There are now over 55,000 articles on DMSO but it is still not recognized as a valuable substance by "the establishment".

He told the audience that DMSO can help Alzheimer patients, stroke and spinal cord injuries. Of 20 patients with head injuries, fourteen survived. Jacobs says he has helped two patients in situations similar to Chris Reeves who walked out after being treated by DMSO shortly after their accidents. The major component of DMSO is demethylsulfone, which is converted into MSM. MSM is a nutritional supplement that relieves pain and reduces inflammation. DMSO is the premier maturation agent for malignant cells and 'pushes' them along to become normal. In rodents, MSM delayed the onset of cancer. DMSO can last a long time but must not be exposed to sunlight. In response to a question

from the audience, he said DMSO could carry herbs if their molecular weight was under 1000.

Arthur Alexander spoke about Hans Nieper's work and the importance of maintaining mineral transport balance. Using Potassium, Magnesium, Aspartic acid, and Selenium. He also mentioned sereptase enzymes, Laetrile, squaline (shark liver oil), bezaldehyde and Venus Fly trap (Carnivora).

Ann's NOTE: Hans Nieper was a German physician who ran a clinic that treated cancer patients with much success.

Dr. Lorraine Day is an orthopedic surgeon at the University of California, SF who was diagnosed in 1992 with invasive ductal carcinoma of the breast. She tried many different approaches including a vegetarian diet and juicing. She got a recurrence and her tumor grew to the size of a grapefruit. She then tried the (Charlotte) Gerson approach, macrobiotics, high-dose Laetrile, 714X, Hoxsey, colonics, chelation and ozone-none of which worked for her.

Then she devised her own plan, which consisted of ten steps: 1) Totally vegan, low protein, fresh fruits, grains and vegetables 2) 75-80% raw foods (for enzymes) 3) Carrots, oranges and apples 4) Exercise to oxygenate the body and eliminate toxins and cholesterol 5) Ten glasses of water a day to decrease blood pressure and reduce allergies 6) Enjoying the outdoors and getting sunlight (she said tumors got twice as hard indoors) 7) Avoidance of caffeine and sugar 8) Not eating foods with labels 9) Reducing stress and getting lots of rest 10) Prayer

Within eight months her tumor shrank and she was completely well in eighteen months. A very upbeat character. She has written at least one book.

Dr. Frederic Douwes, Klinik St. Georg (Germany) spoke about the use of PDT (photodynamic therapy), microwave and radiofrequency hyperthermia. Tumor cells are heat sensitive and can be destroyed by heat. They use super infrared, interstitial short wave brachytherapy as well. They have combined hyperthermia and Govallo. 20-30 patients with brain tumors have benefited from these therapies. With pancreatic patients, they use hyperthermia and low dose chemotherapy as well as complementary therapy. This clinic does offer healthy food. He said they do well with non-small cell lung cancer, cervical, breast and prostrate.

Ann's NOTE: See the section under Meeting Summaries for a talk by Dr. George O'Oclock. A link to the Klinik is under Gerson and Other Clinics section.

Russel Reiter, PhD (reiter@uthscsa.edu) spoke about his work with melatonin. It is derived from the pineal gland. Some people need more than others do. Your genes determine how much any individual needs. The pineal gland responds to light, which can alter the circadian clock and suppress the actions of the pineal gland. Light does interfere with production of melatonin.

Melatonin can help limit the growth of tumors. Women with estrogen-positive breast tumors tend to have attenuated melatonin compared to same age healthy women. He postulates a relationship between melatonin and breast, prostate and hepatoma patients. Melatonin can scavenge free radicals and may be more effective than anti-oxidants.

Some foods can provide melatonin: oats, sweet corn, rice, ginger and bananas were mentioned. In terms of light, a red light will not interfere in production of melatonin. Melatonin could be used with Adriamycin and cisplatin (two chemo drugs) but it may reduce the effect of radiation therapy. He personally takes 3 mgs per night but has taken up to 300 mgs with no ill effects. He suggested that good sources of Melatonin come from Nature's Way, Source Natural, Nutricology and NatureMade.

Ann's NOTE: See Ann's Bio for her use of Melatonin. Also, he will be a speaker at a workshop on Circadian Rhythm in March 2000 sponsored by the National Action Plan on Breast Cancer.

Remember Ann is NOT A Doctor and has NO medical training.

USE OF CYCLOOXYGENASE (COX) 2 INHIBITORS *CELECOXIB (CELEBREX)*OR *ROFECOXIB (VIOXX) IN VETERANS*

The following guidelines are based on current literature and expert opinion from clinicians. It is expected that significant, new information will be forthcoming in this drug class. Thus, the following recommendations are dynamic and will be revised as new clinical data becomes available. These guidelines are not intended to interfere with clinical judgement. Rather, they are intended to assist practitioners in providing cost effective, consistent, high quality care.

CELECOXIB AND ROFECOXIB are NSAIDs (non-steroidal anti-inflammatory drugs) that primarily inhibit cyclooxygenase (COX) 2, and avoid inhibition of COX -1 at therapeutic concentrations [1,2]. COX -1 is produced constitutively in most tissues and is responsible for prostaglandin synthesis important for the maintenance of the gastric mucosal barrier and platelet aggregation. COX -2 is an inducible isoform present at sites of inflammation [3-7]. COX -2 is also present in the kidneys, brain, and reproductive organs and may have some physiologic role in these tissues [4-9]. Celecoxib has been reported to produce a lower rate of endoscopically demonstrated gastroduodenal lesions compared to ibuprofen (800 mg tid), naproxen (500 mg bid), and diclofenac SR (75 mg bid) [1]. Administration of rofecoxib, compared to ibuprofen (800 mg tid), was associated with a lower incidence of gastroduodenal erosions or ulcers upon endoscopy [2]. However, the correlation of endoscopic lesions/ulcers and incidence of clinically serious upper gastrointestinal events is unknown. Data on file (Searle) from open-label celecoxib trials, report an annual incidence of clinically significant GI events of 0.18% in nearly 4500 patients. The Food and Drug Administration predicts 2-4% of patients, taking NSAIDs on a daily basis for 1 year, will experience a symptomatic GI perforation, ulceration or bleeding [43]. In comparative experimental arthritis studies and in epidemiological studies, the annual incidence of serious gastrointestinal complications in non-NSAID users ranges from 0.1%-0.29% [44-46]. Although infrequent, there have been reports of significant upper gastrointestinal bleeding with celecoxib and rofecoxib in controlled and open-label trials. Recently, there have been reports of several deaths and serious gastrointestinal events (bleeding or ulcers) in patients receiving celecoxib within the first 3 months of marketing. However, the causality of these events is unclear. Although the use of highly selective COX -2 inhibitors may result in a lower incidence of gastrointestinal toxicity, it is not known whether other side effects may arise as a result of specific COX -2 inhibition [4-9]. Clinical trials with celecoxib and rofecoxib have not demonstrated any benefit of these agents over currently available NSAIDs with regard to renal effects [1,2,42]. Given the lack of published data, celecoxib and rofecoxib should be considered second-line NSAID therapy for RA and OA, reserved for patients at high risk for adverse outcomes to traditional NSAIDs.

OTHER COX-2 SELECTIVE AGENTS .In addition to the newly marketed COX -2 agents, several other available NSAIDs have relative COX -2 selectivity (e.g. etodolac, nabumetone) [6,13-15]. More importantly, the non-acetylated salicylates (e.g. salsalate) have no measurable effects on COX -1 activity in the stomach [14]. In addition, non-acetylated salicylates do not affect platelet aggregation [16]. Several other factors, aside from selective COX -2 inhibition, may play a role in lessening the risk of GI toxicity of NSAIDs including nonacidic prodrugs (nabumetone), shortened half-life, and low or absent enterohepatic recirculation (etodolac, nabumetone) [10-12]. Endoscopic studies of patients taking salsalate or etodolac (Lodine) indicate low rates of gastric lesions compared to several NSAIDs (Table 1). Fries, et al developed a summary index of drug-induced side effects, laboratory abnormalities, and drug-related hospitalizations referred to as a GI toxicity index (GI TI) [23-25], which has been validated using patients in the Arthritis, Rheumatism and Aging Medical Information System Post Marketing Surveillance Program (ARAMIS PMS) database. The purpose of this database is to prospectively monitor status and outcomes of patients with rheumatoid (RA) and osteoarthritis (OA), drug side effects, and economic impact of illness. The PMS database exists within the ARAMIS database, which is a prospective, observational, noninterventional cohort of patients with chronic disease [27]. Salsalate ranked as having the lowest GI TI [26]. Future ARAMIS PMS reports will include the GI TI for etodolac and nabumetone. Serni reviewed four worldwide postmarketing surveillance studies (4 weeks to 1 year in duration) in nearly 8400 patients with OA or RA receiving etodolac and reported an overall incidence of confirmed ulcers of 0.06% [28]. Data from double-blind and open-label trials (2-6 weeks in duration), enrolling more than 55,000 patients receiving etodolac, demonstrated an incidence of serious gastrointestinal events ranging from 0.04-0.3% [29-30]. Several endoscopic trials have been published supporting nabumetone's safer GI toxicity profile compared to ibuprofen and naproxen [50-52]. However, the dose of nabumetone used in these studies was only 1000 mg daily. A recent randomized trial of 1203 patients with osteoarthritis of the hip or knee and a history of endoscopically documented gastric,

pyloric-channel, duodenal ulcer, or 10 or more erosions in the stomach or duodenum found Arthrotec 75 bid (misoprostol 200 mcg+diclofenac 75 mg) superior to nabumetone 1500 mg qd with regard to 6-week incidence of gastric ulcers (1% vs 9%, p<0.05) [32]. Data on file (SmithKline Beecham) from randomized, double-blind, controlled and open label trials with nabumetone show a rate of serious GI complications of 0.10 per 100 patient-years compared to 1.33 per 100 patient-years for traditional NSAIDs. When evaluating the same data, using only randomized controlled trials ranging from 3 to 6 months in duration, in 5,200 patients receiving nabumetone, the incidence of serious GI complications was 0.02% (data on file). In a four week, double-blind, placebo-controlled trial, 270 patients with active osteoarthritis of the knee were randomized to receive etodolac 400 mg bid, nabumetone 1500 mg qd or placebo to compare the safety and efficacy of these agents [34]. The authors found that etodolac had the earliest onset of action and, at the final visit, the greatest improvements in patientsí and investigatorsí global assessments of disease severity (p<0.05). There were no differences between groups in side effects with the exception of more frequent hypokalemia with nabumetone. Although head-to-head, long-term clinical trials comparing the efficacy and safety of etodolac and nabumetone are lacking, it appears that both can be considered "safer NSAIDs". Since etodolac has recently become available as a price-competitive generic product and offers a safer alternative to current formulary NSAIDs, it was added to the VA National Formulary for those patients considered to be at moderate risk for NSAID-induced GI injury.

ASSESSING NSAID GI RISK . A simple self-assessment tool, developed from the ARAMIS database, helps to quantify the risk of NSAID-related gastrointestinal complications in patients with OA or RA (G. Singh, see appendix 1). Risk of NSAID-related events is graded from 1 (lowest) to 4 (highest). Patients in risk levels 1 or 2 may receive a nonselective formulary NSAID (ibuprofen, naproxen, salsalate, sulindac, piroxicam, tolmetin). Those in risk group 3, who take NSAIDs for less than 30 days or intermittently, may also receive a nonselective formulary NSAID. Patients in risk group 3, who take NSAIDs chronically, should receive a therapeutic trial of salsalate prior to prescribing a COX -2 **inhibitor**. Although limited, extant data support etodolac's lower incidence of significant GI complications compared to traditional NSAIDs. Therefore, consideration should be given to using etodolac or salsalate prior to a COX -2 **inhibitor** in patients in risk group 3 (chronic user). Patients in risk group 4 may receive salsalate or a COX -2 specific agent. Patients with a history of hospital admission for a serious gastrointestinal event or those receiving warfarin may receive salsalate or a COX -2 without having to calculate a GI Score [41]. The efficacy of salsalate in treating rheumatoid arthritis has been documented in several trials (Table 2).
The following individuals are considered to be at a higher risk of upper GI events associated with NSAIDs

and may be candidates for acetaminophen (OA), salsalate, celecoxib or rofecoxib [36-40] . **However, no data exist in high-risk patients receiving celecoxib or rofecoxib, so extreme caution must be used, as with other NSAIDs, in these individuals. It is imperative to determine whether patients truly need treatment with a NSAID or COX-2 inhibitor prior to their initiation.** Other options, such as non-pharmacologic aids (e.g. physical therapy, assistive devices), topical analgesics (e.g. capsaicin), and other forms of non-NSAID analgesia (e.g. codeine, propoxyphene) should be considered. NSAID overuse is common and can be dangerous. A recent retrospective chart review included patients treated with NSAIDs or **aspirin** and admitted with an upper gastrointestinal bleed, perforation or gastric outlet obstruction; an indication for NSAID or **aspirin** therapy was identified in only 55% [47]. In this study, over 40% of patients receiving NSAIDs or **aspirin** were at high risk for complications from NSAIDs.
Individuals with a higher risk for NSAID-induced GI injury:

1. Prior history of a **serious** gastrointestinal event (**hospital admission** for gastroduodenal perforation, ulcer or bleed). Patients with osteoarthritis must fail treatment with acetaminophen 4000 mg qd. If an NSAID must be used, treatment options include salsalate, a non-cox-2 selective NSAID (formulary-nonselective NSAID) with cytoprotection (e.g. PPI or alternatively, misoprostol or famotidine- *not on VA National Formulary-see page 5*) or a COX-2 **inhibitor**.

2. Concurrent use of warfarin (Reinforce to patients to report any signs or symptoms of bleeding. In addition, patients and their INRs should be monitored more closely when any new drug is initiated). Patients should fail acetaminophen (osteoarthritis) 4000 mg qd **and** salsalate 1500 mg bid (osteoarthritis and rheumatoid arthritis) prior to receiving a COX -2 **inhibitor**. Since marketing, there have been reports of increased INR and subsequent bleeding as a result of using the combination of warfarin and celecoxib. Concurrent use of rofecoxib and warfarin resulted in an 8-11% increase in INR in single and multiple dose studies.

Patients not having a history of hospital admission for a significant gastrointestinal event or those not receiving warfarin must have a GI Score (see appendix 1) calculated in order to identify their risk level prior to receiving a COX -2 inhibitor.

The use of low dose aspirin (equal to or less than 325 mg qd) may reduce or eliminate any gastrointestinal protective benefit of the COX-2 inhibitors (see discussion of the CLASS trial below).

WHEN NOT TO USE A COX -2. Patients with an allergy to sulfonamides should NOT receive celecoxib. Dyspepsia with NSAIDs is not an indication for a COX -2 inhibitor. Cyclooxygenase-2 inhibitors can also cause dyspeptic symptoms. Furthermore, lack of response to NSAIDs is not an indication for COX -2 inhibitors since they have not been shown to be superior to traditional NSAIDs. Patients receiving lansoprazole, omeprazole or misoprostol will not be considered for treatment with a cyclooxygenase-2 inhibitor since all of these agents, combined with traditional NSAIDs, have been shown to decrease the risk of NSAID-induced GI toxicity in high-risk patients [33,34,35]. The exception is for patients treated with warfarin that require an NSAID, and have failed a therapeutic trial of salsalate, and require a PPI for GERD, ZE, etc.

LOW DOSE ASPIRIN COMBINED WITH A COX-2. Recently, there have been 2 articles published questioning the gastrointestinal safety of **low dose aspirin**. In addition, the CLASS (Celecoxib Long-term Arthritis Safety Study) was published. In the CLASS trial, the use of **low dose aspirin** (for cardioprotection) was permitted in both the celecoxib and NSAID (ibuprofen and diclofenac) groups.

In the first article, Cryer, et al [35], studied the effects of 3 **low** doses of **aspirin** in 29 healthy volunteers. The investigators attempted to evaluate whether there was a minimally effective **dose** of **aspirin** in which thromboxane was maximally inhibited without causing gastric mucosal injury. Each subject underwent gastroduodenal endoscopy at baseline, 1.5 and 3 months to determine the effects of 10 mg, 81 mg, and 325 mg of **aspirin** daily. At the time of endoscopy, biopsies were taken from the gastric and duodenal mucosa to determine the prostaglandin content 2 hours after the **aspirin dose**. Subjects were given the option of also undergoing flexible sigmoidoscopy at baseline and 3 months in order to visualize and obtain biopsy specimens from the rectal mucosa. Serum thromboxane levels were measured at baseline, 1.5 and 3 months.

All three doses of **aspirin** resulted in gastric injury with one 5-mm gastric ulcer observed in the antrum of the stomach at 1.5 months in a patient receiving 10 mg of **aspirin** daily. Three other antral ulcers were noted after 3 months in 2 patients receiving 325 mg of **aspirin** daily (one patient had one 5-mm ulcer, the other had 2 ulcers 8-mm and 6-mm). The authors note that gastric injury appeared to be dose-related, however the differences were not significant. As for the duodenum, injury was only observed with the 325 mg **dose**. No injury was noted in the rectum with any of the **aspirin** doses.

When the gastrointestinal prostaglandin content was measured from the gastrointestinal biopsies, all 3 doses of **aspirin** reduced gastric prostaglandin content similarly (34-44% of baseline levels). Duodenal prostaglandins were reduced significantly only in the 81 mg and 325 mg groups and rectal prostaglandin content was decreased only in the **aspirin** 325 mg daily group.

Serum thromboxane levels were reduced in the 10 mg, 81 mg, and the 325 mg **aspirin** groups to 38%, 2% and 3% of baseline values, respectively.

The authors concluded that they were unable to identify a **dose** of **aspirin** that would provide maximal inhibition of thromboxane synthesis while minimizing the risk of gastric injury. Furthermore, doses of **aspirin** as **low** as 10 mg daily resulted in gastric injury while only modestly reducing thromboxane levels. The authors question the long-term safety of even 10 mg of **aspirin** daily.

The second article [36] was a meta-analysis undertaken to assess the incidence of gastrointestinal complications associated with long-term **aspirin**. In addition, to determine whether **dose** reduction and formulation alter the incidence of those gastrointestinal complications.

Twenty-four randomized controlled trials of **aspirin** were included in the analysis for a total of 65,987 primarily male patients. Doses of **aspirin** ranged from 50-1500 mg daily. Indications for **aspirin** included healthy subjects, atrial fibrillation, myocardial infarction, secondary stroke prophylaxis, etc. In all 24 trials, patients were not included if they had a history of peptic ulcer disease, prior gastrointestinal hemorrhage, or any other contraindication for **aspirin** therapy.

Overall, gastrointestinal hemorrhage occurred in 2.47% of those taking **aspirin** versus 1.42% of those taking placebo. The pooled odds ratio for gastrointestinal complications with **aspirin** was 1.68 (95% CI, 1.51-1.88; $p<0.0001$). The author also noted the number of patients needed to harm, based upon treatment with **aspirin** for an average of 28 months, was 106.

Data, with lower doses of aspirin (50-162.5 mg daily), were analyzed separately for a total of 49,927 patients. Gastrointestinal hemorrhage occurred in 2.3% of patients taking aspirin versus 1.45% of those taking placebo. The pooled odds ratio for gastrointestinal hemorrhage with aspirin was 1.59 (95% CI, 1.4-1.81; p<0.0001).
The authors performed meta-regression to assess for a possible correlation between daily dose of aspirin and risk of gastrointestinal hemorrhage. They were able to determine that for every 100 mg reduction in aspirin dose, the incidence of hemorrhage was reduced by 1.5% which was not statistically significant (p=0.3).

The authors concluded, from their review of the literature, that there is no evidence to support the notion that reducing daily aspirin dose or use of a modified-release form of aspirin translates into lower risk of gastrointestinal hemorrhage. Furthermore, providers and their patients need to consider the risk-benefit ratio of long-term aspirin administration.

The CLASS (celecoxib long-term arthritis safety study) [37] included 8000 patients with osteoarthritis or rheumatoid arthritis. These patients were randomized to receive celecoxib 400 mg bid, ibuprofen 800 mg tid or diclofenac 75 mg bid for a minimum of 6 months. The use of low dose aspirin was permitted during the trial with approximately 20% of patients in each group receiving it (data for diclofenac and ibuprofen were grouped together and referred to as the NSAID group). The primary endpoint of the CLASS trial was complicated upper gastrointestinal events (UGI) (defined as perforation, obstruction, or GI bleeding). The secondary endpoint was symptomatic ulcers combined with complicated UGI events.
Overall, there was no statistically significant difference in the incidence of complicated UGI events between the celecoxib and the NSAID group (0.76% vs. 1.45%, respectively; RR 0.53; 95% CI 0.26-1.11; p=0.09). There were statistically fewer symptomatic ulcers in the celecoxib versus the NSAID group (2.08% vs. 3.54%, respectively; RR0.59; 95% CI 0.38-0.94; p=0.02). Patients not taking low dose aspirin had statistically significantly fewer events in the celecoxib versus the NSAID group (complicated UGI events: 0.44% vs. 1.27%, respectively; RR 0.35; 95% CI 0.14-0.98; p=0.04; symptomatic GI events: 1.4% vs. 2.91%, respectively; RR 0.48; 95% CI 0.28-0.89; p=0.02). However, patients taking low dose aspirin had no difference in either complicated UGI or symptomatic GI episodes (complicated UGI: 6 events in both groups p=0.92; symptomatic GI: 14 events in the celecoxib versus 17 in the NSAID group p=0.49). Moreover, the use of low dose aspirin, combined with a nonselective NSAID (ibuprofen or diclofenac), did not significantly increase GI ulcer complications in patients receiving nonselective NSAIDs (ibuprofen or diclofenac) alone. Note that data from the CLASS trial was annualized, based upon 6-month-results. About

57% of patients completed 6 months of the trial with just over 40% of those randomized to celecoxib and 44% of those randomized to the NSAID group withdrawing from the trial early due to adverse events, lack of efficacy, and protocol violation.
Although data are limited, it appears from this trial that the use of low dose aspirin may reduce or eliminate any gastrointestinal protective benefit of the COX-2 inhibitors. Furthermore, the use of low dose aspirin with ibuprofen or diclofenac did not seem to increase the GI toxicity of these agents significantly.
Although well documented in previous studies, it can be concluded from the studies above that the use of low dose aspirin is associated with an increased risk for gastrointestinal hemorrhage compared with nonusers of aspirin. In the investigation by Cryer, et al, doses as low as 10 mg of aspirin daily were associated with a reduction in gastric prostaglandin content and one gastric ulcer, however no placebo group was included. In the CLASS trial, when analyzed separately, users of low dose aspirin did not seem to gain any gastrointestinal protective benefit while receiving the cyclooxygenase 2-inhibitor, celecoxib, compared to those in the NSAID (ibuprofen and diclofenac) groups. Interestingly, no significant increase in gastrointestinal toxicity was noted in those receiving low dose aspirin in combination with a NSAID.
Therefore, at present, there is little data to support the argument that patients on aspirin (any dose) will achieve any gastrointestinal protective benefit from the COX-2 inhibitors compared to nonselective NSAIDs. Furthermore, the use of aspirin appears to significantly reduce or eliminate any potential gastric safety benefit of the COX-2 inhibitors. Providers are cautioned to consider the risk-benefit ratio of prescribing prophylaxis with low dose aspirin in their patients.

GASTROINTESTINAL CYTOPROTECTION: REDUCING THE RISK OF NSAID-ASSOCIATED UGI COMPLICATIONS. Several options, to reduce the risk of NSAID-associated GI damage in patients requiring treatment with NSAIDs, currently exist and include combining a proton-pump inhibitor (PPI), misoprostol, or high-dose histamine-2 receptor blockers with a nonselective NSAID or switching to a COX-2 inhibitor. Data from the CLASS (see page 4 for discussion) trial has raised question with regard to the continued GI safety benefit of the COX-2 inhibitors compared to the nonselective NSAIDs in patients receiving treatment with low dose aspirin. Recently, lansoprazole has received FDA approval for the healing and prevention of NSAID-associated ulcers based upon endoscopic data, although the correlation of endoscopically determined ulcers/lesions and incidence of serious upper GI complications is not known.

MISOPROSTOL (CYTOTEC): THE MUCOSA TRIAL

Investigators of the MUCOSA Trial attempted to determine whether misoprostol 200 mcg, administered four times daily, reduced the incidence of serious upper gastrointestinal complications (e.g. perforation, obstruction, GI bleeding) in patients with rheumatoid arthritis taking NSAIDs. This study was a 6- month, randomized, double-blind, placebo-controlled trial in which 8,843 patients were enrolled. Gastrointestinal events were investigated during usual clinical care (no planned endoscopies or other GI procedures) based upon spontaneous reporting. A second objective was to identify whether certain patients were at increased risk for NSAID-associated gastrointestinal events.
Patients in the placebo group experienced more serious ulcer complications documented by surgery,

endoscopy, or radiography than those receiving misoprostol (33 of 4439 vs. 16 of 4404, respectively; odds ratio 0.487; [95% CI 0.268 to 0.787; p=0.012]) resulting in a 51% reduction in events. In the misoprostol group, perforated ulcers and ulcer-induced gastric outlet obstruction were decreased 10-fold compared to those patients receiving placebo (1 of 4404 vs. 10 of 4439; odds ratio 0.101[95% CI 0.013-0.787; p=0.012]). Combined events, including complicated events and confirmed, symptomatic ulcers, occurred statistically significantly less often in the misoprostol compared to placebo group (25 of 4404 vs. 42 of 4439; odds ratio 0.598 [95% CI 0.364-0.982; p=0.049]) resulting in a 40% reduction in event risk. When the data was analyzed for bleeding events, with or without confirmation of active ulceration, 33 of 4404 misoprostol vs. 51 of 4439 placebo recipients experienced bleeding episodes resulting in a 35% reduction in bleeding in the misoprostol vs. placebo group (odds ratio 0.650 [95% CI 0.418 to 1.009; p=0.062]) which was not statistically significant.

USE OF CYCLOOXYGENASE (COX) 2 INHIBITORS *CELECOXIB* (*CELEBREX*) OR *ROFECOXIB* (*VIOXX*) *IN VETERANS*

The investigators determined that age 75 years or greater, history of peptic ulcer disease, history of gastrointestinal bleeding, and history of cardiovascular disease placed individuals at a greater risk of serious NSAID-associated upper GI events. They were unable to correlate use of corticosteroids, arthritis disability score or gender with increased risk for significant events.
The authors concluded that misoprostol reduces the risk of serious upper GI events including perforation,

obstruction or bleeding in older patients with rheumatoid arthritis taking NSAIDs.
Cumulative endoscopic evidence, in patients receiving misoprostol compared to placebo, suggests a dose-

response relationship in gastric ulcer formation with misoprostol 800 mcg daily being associated with the lowest risk (RR 0.18; 95% CI 0.11-0.28) and 400 mcg daily with a relative risk of 0.38 (95% CI 0.3-0.49) reaching a statistical difference (p=0.0055). Misoprostol 600 mcg daily was not different than either the 400 or 800 mcg dose [38]. Therefore, a dose of at least 600 mcg daily is needed for gastric protection.

PROTON-PUMP INHIBITORS: Lansoprazole (Prevacid) has recently received FDA approval for the treatment of NSAID-associated gastric ulcer in patients who continue NSAID use. In addition, it was granted FDA approval for reducing the risk of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer and who continue to require treatment with NSAIDs. The recommended dose of lansoprazole for healing is 30 mg qd and for reducing risk of NSAID-associated GI events is 15 mg qd. All of the following studies utilize endoscopy to document their study endpoints recognizing that the correlation of endoscopic ulcers/lesions with the incidence of clinically serious upper gastrointestinal events is not known.

Clinical Trial	Treatment Group	Results	Comments
Yeomans ND, et al [44] I, MC, R, DB 541 patients 4 to 8 weeks 432 patients 6 months (Astra) Endpoint: Complete healing of ulcer(s) (gastric or duodenal) or significant ↓ in # of erosions and minimal or no symptoms of dyspepsia.	Inclusion required ulcer(s) or 10 or more erosions in the stomach or duodenum and continued need for NSAID treatment. Healing Phase: (4-8 weeks) -RAN 150 mg bid (n=174) -OME 20 mg qd (n=174) -OME 40 mg qd (n=187) Maintenance Phase: (6 months) -RAN 150 mg bid	Healing Phase: Treatment was successful in 63% of those receiving RAN compared to 80% and 79% of those receiving OME 20 and 40 mg, respectively (p=or< 0.001). The rate of healing for all types of lesions was statistically faster during the 8 weeks (p<0.001) for both doses of OME compared to RAN. Maintenance Phase: At the end of 6 months, there were 59% of patients receiving RAN compared to 72% of those in the OME group in remission (p=0.004). -At 8 weeks, most patients had none or only mild symptoms of dyspepsia. There were no differences between groups.	-ADEs were similar between groups. -After 10 days of maintenance therapy on OME, 1 patient developed a bleeding duodenal ulcer and was hospitalized. -Gastric ulcers recurred 5.2% of patients on OME vs. 16.3% of those on RAN. Duodenal ulcer recurred in 0.5% on OME vs. 4.2% on RAN. -This study included patients that had evidence of endoscopic ulcers or lesions at baseline theoretically placing them at a higher risk of NSAID-associated ADE.

	-OME 20 mg qd	**Healing and Maintenance:** **OME 20 and 40 mg>RAN**	

ADE=adverse effects, DB= double-blind, I=International, LAN=Lansoprazole, MC=multicenter, MIS=misoprostol, OME=omeprazole, PC=placebo-controlled, PLA=placebo, R=randomized, RAN=ranitidine
(Responsible for finding)

USE OF CYCLOOXYGENASE (COX) 2 INHIBITORS *CELECOXIB (CELEBREX)*OR *ROFECOXIB (VIOXX) IN VETERANS*

Clinical Trial	Treatment Group	Results	Comments
Hawkey, CJ , et al [49] I, MC, R, DB, PC (maintenance phase) 935 patients 4 to 8 weeks 732 patients 6 months (Astra) **Endpoint:** same as previous study by Yeomans, et al.	Inclusion required ulcer(s) or 10 or more erosions in the stomach or duodenum and continued need for treatment with NSAIDs. **Healing Phase:** (4-8 weeks) -MIS 200 mcg qid (n=298) -OME 20 mg qd (n=308) -OME 40 mg qd (n=315) **Maintenance Phase:** (6 months) MIS 200 mcg bid OME 20 mg qd PLA qd	**Healing Phase:** At 8 weeks, 71% of MIS, 76% of OME 20 mg, and 76% of OME 40 mg reached the endpoint resulting in no significant difference between groups. **Maintenance Phase:** At 6 months, the percentage of patients in remission was 61% in the OME 20 mg group vs. 48% of those taking MIS vs. 27% of those taking PLA. OME vs. MIS p=0.001 OME and MIS vs. PLA p<0.001 **Healing: OME 20 and 40 mg=MIS** **Maintenance: OME>MIS>PLA**	ADE occurred in a higher percentage of patients receiving MIS compared to either dose of OME (no p value listed). -1 perforated duodenal ulcer occurred in a patient receiving PLA during the maintenance phase after 31 days. -32% of patients on PLA developed gastric ulcers during the maintenance phase vs. 10% on MIS and 13% on OME. -This study included patients that had evidence of endoscopic ulcers or lesions at baseline theoretically placing them at a higher risk of NSAID-associated ADE. -The authors note a statistically higher percentage of healed gastric ulcers in the OME 20 mg group compared to MIS. Duodenal ulcer healing rates were higher in both OME groups vs. MIS. Erosion healing rates were higher in the MIS vs. OME groups.
Agrawal NM, et al [39] MC, R, DB 353 patients 8 weeks (TAP) **Endpoint:** Complete gastric ulcer healing with no evidence of ulcer crater or erosion at ulcer site.	Inclusion required having a nonmalignant gastric ulcer (> or = to 5 mm) diagnosed by endoscopy in patients receiving stable doses of NSAIDs for 30 days or more who continued to need treatment with NSAIDs. -RAN 150 mg bid -LAN 15 mg qd -LAN 30 mg qd	**Ulcer healing:** At 8 weeks, 53% of those receiving RAN, 69% on LAN 15 mg, and 73% of patients on LAN 30 mg experienced complete ulcer healing (p=0.01 for RAN vs. LAN 15 mg) (p=0.009 for RAN vs. LAN 30 mg). Controlling for H pylori status, gastric ulcer healing was similar in infected vs. non-infected patients, however the healing rates were statistically higher in both LAN groups compared to RAN (p ranged from 0.001 to <0.05). **Ulcer healing in those continuing on** **NSAIDs:** **LAN 15 and 30 mg>RAN**	-ADEs were similar across treatment groups and no report of ulcer complications. -No significant difference in healing of gastric ulcers was seen between the 2 doses of LAN. -Trend toward better symptom relief with LAN 15 and 30 mg vs. RAN.

ADE=adverse effects, DB= double-blind, I=International, LAN=Lansoprazole, MC=Multicenter, MIS=misoprostol, OME=omeprazole, PC=placebo-controlled, PLA=placebo, R=randomized, RAN=ranitidine
(Responsible for finding)

USE OF CYCLOOXYGENASE (COX) 2 INHIBITORS *CELECOXIB (CELEBREX)*OR *ROFECOXIB (VIOXX) IN VETERANS*

Clinical Trial	Treatment Group	Results	Comments
Data on File TAP	Inclusion: chronic	At 4, 8 and 12 weeks, use of MIS	-Unpublished data
Pharmaceuticals [40] MC, R, DB, PC 535 patients 12 weeks (TAP)	NSAID users with a history of gastric ulcer but no current gastric or duodenal ulcer and were H. pylori negative with fewer than 25 gastric or duodenal erosions.	resulted in 96, 95, and 93% of patients remaining gastric ulcer free, respectively. As for LAN 15 mg, 90, 86, 80% of patients remained gastric ulcer free at 4, 8, and 12 weeks, respectively. LAN 30 mg resulted in 92, 88, and 82% of patients remaining gastric ulcer free at 4, 8 and 12 weeks, respectively. As for PLA 66, 60, and 51% of patients remained gastric ulcer free at 4, 8, and 12 weeks, respectively while continuing NSAID treatment.	-Included patients with a history of prior ulcer.
Endpoint: Reoccurrence of NSAID-associated ulcers.	-MIS 200 mcg qid -LAN 15 mg qd -LAN 30 mg qd -PLA qd	p<0.0001 for all 3 active groups vs PLA p<0.05 for MIS vs. LAN 15 or 30 mg **Patients remaining gastric ulcer free while continuing NSAIDs:** **MIS>LAN 15 and 30 mg>PLA**	

ADE=adverse effects, DB= double-blind, I=International, LAN=Lansoprazole, MC=Multicenter, MIS=misoprostol, OME=omeprazole, PC=placebo-controlled, PLA=placebo, R=randomized, RAN=ranitidine
(Responsible for funding)

HIGH DOSE HISTAMINE-2 RECEPTOR (H2R) BLOCKERS: All of the following studies utilize endoscopy to document their study endpoints recognizing that the correlation of endoscopic ulcers/lesions with the incidence of clinically serious upper gastrointestinal events is not known. There are no studies comparing the effectiveness of high-dose H2R blocking agents to misoprostol or PPIs in the prevention of NSAID-associated GI ulcers. To date, only famotidine 40 mg bid has been demonstrated to prevent gastric ulcers associated with NSAIDs.

Clinical Trial	Treatment Group	Results	Comments
Taha AS, et al [42] R, DB, PC 285 patients 24 weeks (Merck)	Inclusion: patients with RA (82%) or OA (18%) without peptic ulcers receiving chronic NSAIDs. FAM 20 mg bid (n=84)	Cumulative gastric ulcer incidence was 20% in the PLA group, 13% in the FAM 20 mg group, and 8% in the FAM 40 mg group. (p=0.24 FAM 20 vs. PLA) (p=0.03 FAM 40 vs. PLA)	-In this study, only 10-16% of patients had a history of a previous ulcer. -No active comparator (misoprostol or a PPI)
Endpoint: Cumulative incidence of gastric or duodenal ulceration at 24 weeks.	FAM 40 mg bid (n=83) PLA bid (n=81) Endpoints were determined by endoscopy at 4, 12 and 24 weeks.	Cumulative duodenal ulcer incidence was 13% in the PLA group, 4% in the FAM 20, and 2% in the FAM 40 mg group. (p=0.04 FAM 20 vs. PLA) (p=0.01 FAM 40 vs. PLA)	
		Prevention of gastric ulcer: FAM 40>FAM 20 or PLA **Prevention of duodenal ulcer: FAM 20 and 40>PLA**	

ADE=adverse effects, DB= double-blind, FAM=famotidine, I=International, LAN=Lansoprazole, MC=Multicenter, MIS=misoprostol, OA=osteoarthritis, OME=omeprazole, PC=placebo-controlled, PLA=placebo, R=randomized, RA=rheumatoid arthritis, RAN=ranitidine
(Responsible for funding)

USE OF CYCLOOXYGENASE (COX) 2 INHIBITORS *CELECOXIB (CELEBREX)*OR *ROFECOXIB (VIOXX) IN VETERANS*

Clinical Trial	Treatment Group	Results	Comments
Hudson N, et al [43] R, DB, PC Healing phase: 104 patients 12 weeks Maintenance Phase: 78 patients 6 months (Merck) Endpoint: Healing phase: Complete healing at 4 and 12 week. Maintenance phase: Cumulative incidence of gastroduodenal ulcers.	Inclusion: patients with RA or OA with gastric or duodenal ulcers receiving chronic NSAIDs. Patients were given the option of stopping or continuing their NSAIDs. Healing: FAM 40 mg bid for 12 weeks (n=104), 16 patients stopped NSAIDs, 88 continued. Maintenance: FAM 40 mg bid (n=39) PLA bid (n=39)	Healing: At 12 weeks, 89% of ulcers in those continuing NSAIDs healed vs. 100% of those stopping NSAIDs. Differences were not statistically significant. Maintenance: Cumulative incidence of gastroduodenal ulcers at 24 weeks was 53.5% (95% CI 36.6%-70.3%) for the PLA group vs. 26% (95% CI 12.1%-39.9%) for the FAM group (p=0.011). Healing: Continuing NSAIDs did not delay healing in patients on FAM Maintenance: FAM>PLA for preventing recurrence of gastroduodenal ulcers.	Gastric ulcer incidence was 41.4%(95% CI 24%-58.7%) in the PLA compared to 19.1% (95% CI 6.3%-31.9%) in the FAM group (p=0.026). -Incidence of duodenal ulcer showed a trend toward reduced incidence in the FAM group vs. PLA but was not statistically significant. -No active comparator -Patients all with current ulcer theoretically placing them at higher risk for NSAID-induced GI injury.
WoldeS, et al [44] R, DB, PC 30 patients 12 months (Glaxo) Endpoint: Recurrence of gastric or duodenal ulcer	Inclusion: patients with RA and a history of gastric and/or duodenal ulcers who required regular use of NSAIDs. Endoscopy was performed at baseline, 6 and 12 months. PLA bid Ranitidine 300 mg bid	Duodenal ulcers recurred in 4 of the 10 patients on PLA but none of the 10 patients receiving RAN (p=0.04; 95% CI fi0.88 to fi0.12). Gastric ulcers recurred in 6 patients in the PLA group and 3 patients in the RAN group (p=0.18; 95% CI fi0.72-0.12). Prevention of: duodenal ulcers: RAN>PLA gastric ulcers: RAN=PLA	Recruitment was slower than anticipated so study was stopped after 3 years. No active comparator. Small sample size.

ADE=adverse effects, DB= double-blind, FAM=famotidine, I=International, LAN=Lansoprazole, MC=Multicenter, MIS=misoprostol, OA=osteoarthritis, OME=omeprazole, PC=placebo-controlled, PLA=placebo, R=randomized, RA=rheumatoid arthritis, RAN=ranitidine
(Responsible for funding)

COX-2 INHIBITORS: CLASS [45] AND VIGOR [46] TRIALS

For discussion of the CLASS trial, please see the section regarding use of a COX-2 combined with **low dose aspirin** starting on page 3.
The VIGOR or Vioxx Gastrointestinal Outcomes Research Trial is a study in which 8,076 patients with rheumatoid arthritis were enrolled and randomized to receive treatment with rofecoxib 50 mg qd or naproxen 500 mg bid for 1 year (median follow up was 9 months). The primary endpoint was confirmed upper GI events (e.g. gastroduodenal perforation or obstruction, upper GI bleeding, and symptomatic ulcers). A secondary endpoint was confirmed complicated events (e.g. perforation, obstruction and severe upper GI bleeding). The use of **low dose aspirin** was not allowed.
The efficacy of rofecoxib vs. naproxen was found to be similar and withdrawal due to lack of efficacy was not significantly different between groups.
The number of confirmed upper GI events was 2.1/100 patient-years in those receiving rofecoxib vs. 4.5/100 patient-years in those receiving naproxen (relative risk, 0.5; 95% CI 0.3-0.6; p<0.001). The rate of

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confirmed complicated events was 0.6/100 patient-years taking rofecoxib vs. 1.4/100 patient-years in those taking naproxen (relative risk, 0.4; 95% CI 0.2-0.8; p=0.005) resulting in both endpoints occurring significantly less often in the group receiving rofecoxib compared to naproxen.
During the trial, an unexpected higher number of myocardial infarctions (MI) were observed in the rofecoxib arm of the study compared to the naproxen arm (0.4 vs. 0.1, relative risk 0.2; 95% CI 0.1-0.6). However, there was no significant difference in the rate of mortality between groups being 0.5% in the

rofecoxib vs. 0.4% in the naproxen group. There was also no difference in the rate of mortality from cardiovascular causes occurring at a rate of 0.2% in both groups. Ischemic cerebrovascular events were reported in 0.2% of patients for either group. Investigators noted that 4% of patients, participating in VIGOR, met the FDA criteria for secondary cardiac prophylaxis with **aspirin** (e.g. prior myocardial infarction, angina, stroke, transient ischemic attack, cardiac bypass or angioplasty), however were not taking **aspirin**. Of the patients experiencing a myocardial infarction, that 4%(with a prior cardiac history) accounted for 38% of the patients having an MI during the study. When the data was evaluated, excluding that 4% of patients, there was no observed statistical difference in the incidence of MI between groups (0.2% rofecoxib vs. 0.1% naproxen). The authors comment that there was no correlation between hypertension and MI, noting that only 1 patient experienced both. They attribute the lower risk of MI, seen in the naproxen group, to naproxenís ability to inhibit the production of thromboxane (by 95%) and inhibit platelet aggregation (by 88%) and maintain this effect throughout its dosing interval.
The authors concluded that although efficacy was similar, treatment with rofecoxib resulted in a

significantly lower incidence of clinically meaningful upper GI events compared to naproxen in patients with rheumatoid arthritis. Furthermore, the reduced incidence of myocardial infarction, observed in the naproxen group, requires further evaluation in larger studies.

CONCLUSION. Misoprostol (800 mcg/day) and the COX-2 inhibitors (without concurrent **aspirin** use) are the only agents that have been shown to reduce the incidence of NSAID-associated ulcer complications in randomized studies. Furthermore, evidence from endoscopic studies supports the use of PPIs (omeprazole and lansoprazole) and high-dose H2R blockers (famotidine 40 mg bid- *not on VA National Formulary*) for the prevention of gastric and duodenal ulcers in patients receiving NSAIDs. Based on the available evidence, the PBM/MAP make the following recommendations:

1. INDIVIDUALS WHO ARE AT HIGH RISK FOR NSAID-INDUCED ULCERS BUT WHO REQUIRE NSAIDS.

For preventing complications in patients who are at high-risk for NSAID-induced ulcers but who require NSAIDs, salsalate (which does not inhibit COX-1) is preferred as first-line therapy. Second line alternatives include combining a nonselective NSAID (e.g. ibuprofen, naproxen, etc) with appropriate gastric cytoprotection (e.g. PPI, misoprostol, famotidine- *see number 3 below)* or using a COX-2 **inhibitor** (celecoxib or rofecoxib).

2. INDIVIDUALS AT HIGH RISK FOR NSAID-INDUCED ULCERS, REQUIRE NSAIDS, BUT ARE RECEIVING CARDIOVASCULAR PROPHYLAXIS WITH LOW DOSE ASPIRIN.

Based on data from the CLASS study (page 4), adding usual cardioprotective doses of **aspirin** (e.g., 81 mg or 325 mg daily) to a COX-2 **inhibitor** (or, presumably, salsalate) reduces or eliminates the GI safety benefit. More specifically, the celecoxib/**aspirin** combination appeared to increase the risk of GI injury to the same level (about 2%) as the nonselective NSAID group with or without **aspirin**. Therefore, patients at high risk for NSAID-induced ulceration should not be considered to be at a lower risk when a COX-2 specific agent is combined with **aspirin**. As a result of this data, although limited, the PBM/MAP do not recommend the combination of a COX-2 **inhibitor** plus **aspirin** in high-risk patients because the safety benefit may be reduced or lost.

3. INDIVIDUALS AT HIGH RISK FOR NSAID-INDUCED ULCERS, REQUIRE NSAIDS, BUT ARE RECEIVING CARDIOVASCULAR PROPHYLAXIS WITH LOW DOSE ASPIRIN.

In patients who are at high-risk for NSAID-induced gastropathy, receiving **low dose aspirin** and requiring NSAIDs, a nonselective NSAID should be combined with gastroprotective therapy. Based upon the available evidence, dosing complexity, potential side effects and cost, a PPI

(lansoprazole 15 to 30 mg daily) is the preferred means of prophylaxis. Misoprostol (at least 200 mcg tid) and high-dose famotidine (40 mg bid- *not on VA National Formulary)* are alternatives for those patients who require prophylaxis but cannot tolerate a PPI.

DOSAGE AND ADMINISTRATION
Celecoxib (Celebrex)

Osteoarthritis: 100 mg bid or **200 mg qd** (Preferred dose is 200 mg qd since the doses were equally beneficial). Rheumatoid Arthritis: 100 mg to 200 mg bid (The doses were equal in their effectiveness, however some patients derived additional benefit from the 200 mg bid).
Rofecoxib (Vioxx)

Osteoarthritis: **12.5 mg** qd. Some patients may receive additional benefit from 25 mg qd.

CONCLUSIONS
Because published data are lacking and cost is significantly greater than formulary NSAIDs, celecoxib and rofecoxib should be considered second-line NSAIDs for the treatment of RA and OA, reserved for patients at high risk for adverse outcomes from traditional NSAIDs. In patients with osteoarthritis, felt to be at high risk for NSAID-induced GI toxicity, consideration should be given to using acetaminophen or other

therapeutic options prior to an NSAID. In patients requiring treatment with a NSAID, at low risk for GI toxicity, a non- COX-2 selective formulary NSAID (e.g. ibuprofen, naproxen salsalate, sulindac, piroxicam, tolmetin) is recommended. In patients requiring treatment with a NSAID, at moderate risk for NSAID GI injury, a trial of salsalate or etodolac should be attempted as first line therapy. In those patients requiring NSAID therapy, at highest risk of GI toxicity, treatment options include salsalate, a non- COX- 2 selective formulary NSAID with cytoprotection (e.g., PPI, misoprostol, famotidine- *not on VA National Formulary)* or a COX -2 Inhibitor. Data from the CLASS trial suggests, that in those individuals receiving prophylaxis with low dose aspirin (less than or equal to 325 mg qd), any GI protective benefit of the COX-2 inhibitors over NSAIDs may be reduced or eliminated. The use of low dose aspirin in combination with nonselective NSAIDs (ibuprofen or diclofenac) did not appear to significantly increase the risk for GI toxicity. As a result of this data, although limited, the PBM/MAP do not recommend the combination of a COX-2 Inhibitor plus aspirin in high-risk patients because the safety benefit may be reduced or lost. In those high-risk patients receiving cardiovascular prophylaxis with low dose aspirin and requiring NSAIDs, nonselective NSAIDs should be combined with lansoprazole because of the available evidence, ease of administration, low occurrence of side effects and cost of therapy compared to misoprostol or famotidine. However, misoprostol and famotidine 40 mg bid (not on VA national formulary) can be considered as alternatives to lansoprazole in these high-risk individuals. As with other NSAIDs, extreme caution should be used when prescribing a COX -2 Inhibitor in high-risk patients since no published information exists in these individuals.

Table 1. Salsalate and Etodolac Endoscopic Trials

Clinical Trial	Treatment	Results	Comments
Lanza, et al [9] Healthy subjects Salsalate n=20 Naproxen n=20 (14 days) SB endoscopist, PG	Salsalate 3.5 g qd (divided bid) Naproxen 375 mg bid Normal baseline endoscopy	Gastroduodenal lesions 10% Salsalate group and 55% naproxen group (p=0.002)	A larger number of patients in the salsalate group reported an ADE compared to the naproxen group. The difference was due to reversible tinnitus/hearing loss. No patients withdrew.
Roth, et al [10] Rheumatoid arthritis Salsalate n=18 Naproxen n=21 (3 months) SB endoscopist and rheumatologist, R, PG	Salsalate 1.5 g bid (doses Titrated 2 to 4 g qd) Naproxen 375 mg bid (doses titrated to 500 to 1000 mg qd) Eligible pts if no history of major GI bleed, ulcer >2 cm or diffuse erosions on baseline endoscopy	38% of naproxen treated pts had gastroduodenal lesions compared to none on salsalate. (p=0.003 Wilcoxon signed rank test)	28-29% of patients had a history of gastroduodenal ulcer prior to study entry (no difference between groups). In the naproxen group, only 2/11 patients with prior ulcer developed ulcer/erosion. Median doses: salsalate 1.5 g bid, naproxen 375 mg bid. No difference in ADEs except for reversible tinnitus or hearing loss with salsalate.
Scheiman, et al [11] Healthy subjects Salsalate n=10 Enteric-coated ASA n=10 (6 days for each treatment) SB (endoscopist), R, crossover	Salsalate 1.5 g bid EC ASA 650 mg qid Baseline endoscopy; reendoscopy after 6 th day of 1st drug; then 7 day washout period; reendoscopy prior to crossover to 2nd agent, then final endoscopy after 6 th day of 2nd drug.	1 patient (10%) receiving salsalate had a grade 1 lesion. 6 patients (60%) receiving EC ASA developed grade 2 or 3 lesions. (p=0.01 Wilcoxon signed rank test)	3 patients receiving salsalate and 2 receiving EC ASA reported tinnitus. Tinnitus was not associated with serum salicylate level. In addition, there was no correlation between salicylate levels and gastroduodenal ulcers.
Cryer, et al [12] Healthy Volunteers Salsalate n=7 ASA n=7 Placebo n=6 (7.5 days)	Salsalate 1.5 mg bid ASA 975 mg qid Placebo qid Baseline and end of study endoscopy	Endoscopy was scored by region (fundus, antrum, bulb, postbulbar) and the sum of scores were compared (0-4 for each region): 11.6 for ASA vs 4.6 for salsalate and 3.9 for	

DB, PC, R		placebo. Significant differences were noted for salsalate or placebo compared to ASA ($p<0.001$ paired t-test). No difference was noted between salsalate and placebo.	
Taha, et al [redacted] Rheumatoid arthritis Etodolac n=15 Naproxen n=15 (4 weeks) DB, R, PG	Etodolac 300 mg bid Naproxen 500 mg bid Baseline and end of study endoscopy	Mucosal lesions developed in 3 (20%) of etodolac pts vs 8 (53%) of naproxen treated pts ($p<0.05$ Wilcoxon signed rank test)	Patients receiving etodolac required less rescue paracetamol. However the only significant difference between etodolac and naproxen in terms of efficacy was right hand grip strength which was better in the naproxen group.
Lanza, et al [redacted] Healthy volunteers Etodolac 600 mg qd n=12 Etodolac 1000 mg qd n=12 Indomethacin n=12 Ibuprofen n=12 Naproxen n=12 Placebo n=12 (7 days) SB (endoscopist), R, PG	Etodolac 300 mg bid Etodolac 500 mg bid Indomethacin 200 mg qd (divided tid) Ibuprofen 600 mg qid Naproxen 500 mg bid Placebo bid Baseline and end of study endoscopy.	In terms of comparison of indomethacin, ibuprofen and naproxen to etodolac, the incidence of gastric lesions was significantly less with etodolac ($p<0.05$). When etodolac was compared to placebo, there was no significant difference in ulcer formation.	The endoscopist and an independent gastroenterologist reviewed endoscopic photographs in a random sequence for reproducibility of scoring.

ADE=adverse effect; DB=double-blind; bid=twice daily; PC=placebo-controlled; PG=parallel group; pts=patients; qd=daily; R=randomized; SB=single-blind; tid= three times daily

Table 2. Salsalate Efficacy Trials

Clinical Trial (ref) Treatment	Results (statistical test)		Comments
Montrone, et al. [redacted] Rheumatoid arthritis: Salsalate n=23 Piroxicam n=20 (4 weeks) DB, R	Salsalate 1.5 g bid Piroxicam 20 mg qd	Ritchie index, morning stiffness, grip strength, VAS, patient assessment of efficacy. (Wilcoxonis signed-rank and Kruskal-Wallis) Both groups improved significantly from baseline for all measures ($p<0.05$). It was noted that there were no between-drug differences (no p value was provided)	Treatment effectiveness was reported to be fair to good in 75% of piroxicam versus 58% of salsalate treated pts. Four pts in the salsalate group withdrew from treatment (2 tinnitus) and none in the piroxicam group.
Deodhar, et al [redacted] Rheumatoid arthritis: Placebo n=18 Salsalate n=18 Indomethacin n=18 (1 week on each treatment) DB, R, PC, crossover study	Each patient was assigned to a random treatment sequence of placebo, salsalate and indomethacin given tid for 1 week (Total number of patients=18)	Duration of morning stiffness, VAS, articular index, grip strength, patient and physician assessments, patients preference, and ESR. (Studentis t-test for paired values). In all above measures, salsalate and indomethacin were significantly better than placebo ($p<0.05$) except grip strength and ESR. Although no p value is provided, it is noted that there was no difference between indomethacin and salsalate except duration of morning stiffness was less with salsalate.	15 patients completed the study. 2 pts on placebo withdrew due to severe pain, and 1 on salsalate withdrew due to tinnitus.
Bombardier, et al. [redacted] Rheumatoid arthritis: Salsalate n=143 Diclofenac n=151 (8 weeks) DB, R, PC	Salsalate 2-4.5 g qd (divided bid) Diclofenac 50-150 mg qd (divided tid)	Primary multivariate analysis: p=0.29 (MANOVA) Total painful joint Pain VAS score Physicianis global score 38% of salsalate and 31% of diclofenac pts withdrew due to lack of efficacy, ADE, Lab abnormality, protocol violation, intercurrent illness (see comments).	Mean daily dose: Salsalate 3.55 g, Diclofenac 112 mg Greater percent of pts were on a higher dose of diclofenac compared to salsalate. A greater number of patients reported ADE with salsalate (tinnitus/hearing loss).
Atkinson, et al. [redacted] Salsalate 771 patients 90% Osteoarthritis 9.7% Rheumatoid arthritis 0.3% Both OA and RA (25 day duration) OL, MC, prospective	Salsalate 1.5 g bid If effective, continue dose. If effective, but ADE limits use, decrease by 1 tablet (750 mg). If not effective and no ADE, increase by 1 tablet (750 mg). If not effective and ADE, D/C salsalate. Max. dose 4.5 g qd	Physician assessment of patient improvement and patient satisfaction with therapy were recorded on a clinical evaluation card. All ADE were recorded and graded by the physician in terms of relationship to salsalate admin. (Descriptive statistics were used to analyze data from the clinical evaluation cards. ADE associations were evaluated by chi-square tests and trends by use of rank scores). Patient satisfaction was rated as excellent or good in 67.2-80.7 % of individuals. Mean salsalate dose at 1 [redacted] and 3 [redacted] weeks were approximately 2.9 g for OA and RA.	The objectives of this trial were to prospectively evaluate the use of tinnitus as a method of establishing the best dose of salsalate in routine practice settings. However, there was minimal dose adjustment over the study period. Patient satisfaction increased over the study duration for OA and RA. 6.7% of patients withdrew due to tinnitus (their doses werenit adjusted downward prior to d/c).
McPherson, TC [redacted] Salsalate 182 patients Inflammatory polyarthritis, Osteoarthritis or nonarticular rheumatism	Salsalate 1.5 g bid	To evaluate current status of disease, investigator rated five indices of arthritis: pain, stiffness, joint swelling, limitation of motion, and disability as mild, moderate or severe. Changes from baseline were assessed. At baseline and study completion, both physician	

(15 day duration) OL, MC		and patient independently estimated the global degree of rheumatic disease as mild, moderate or severe. ADEs were recorded. Median improvement of 47% was noted in 79% of patients measured on a summary index.

ADE=adverse effect; DB=double-blind; bid=twice daily; d/c=discontinuation; ESR=erythrocyte sedimentation rate; MC=multicenter; OA=osteoarthritis; OL=open-label; ; PC=placebo controlled; PG=parallel group; pts=patients; qd=daily; RA=rheumatoid arthritis; R=randomized; SB=single-blind; tid= three times daily; VAS=visual analogue scale

USE OF CYCLOOXYGENASE (COX) 2 INHIBITORS *CELECOXIB (CELEBREX)*OR *ROFECOXIB (VIOXX) IN VETERANS*

Appendix 1:
Gastrointestinal Risk Assessment Tool (GI Score):

This scoring tool was developed by Dr G. Singh and Colleagues at Stanford University and is based upon hospitalization data (566 hospitalizations from serious GI injury) from 6,386 patients with rheumatoid or osteoarthritis followed prospectively. The authors used Cox proportional hazard models to determine risk factors. The GI Score is calculated from individual patient responses to 6 questions. Each question is assigned a certain number of points. Once the points have been added up, a GI risk score from 1 to 4 is assigned (1 lowest risk, 4 highest risk). The 6 questions are as follows:

1. How old are you?

Age	Points	Age	Points	Age	Points
<20 years	0	41-45	6	66-70	13
21-25	1	46-50	8	71-75	14
26-30	3	51-55	9	76-80	16
31-35	4	56-60	10	81-85	17
36-40	5	61-65	12	>85 years	18

Points:_____

2. How do you rate your current health status on the following scale?

Health Status	Points
Very Poor	4
Poor	3
Fair	2
Well	1
Very Well	0

Points:_____

3. Has a physician ever told you that you have rheumatoid arthritis (not osteoarthritis or other forms of arthritis)?

No: 0 points Yes: 2 points **Points_____**

4. If you are taking prednisone or other corticosteroid, for how many months have you taken them in the past year?

Months	Points
0	0
1-3	1
4-6	3
7-10	4
11-12	5

Points:_____

5. Have you ever been hospitalized for a stomach or intestinal problem such as bleeding or an ulcer?

(If the answer is yes, skip the next question).
No 0 points Yes: 8 points **Points:_____**

USE OF CYCLOOXYGENASE (COX) 2 INHIBITORS *CELECOXIB (CELEBREX)*OR *ROFECOXIB (VIOXX) IN VETERANS*

6. If no, have you ever had gastrointestinal side effects (heartburn, stomach pain, nausea, vomiting) when taking NSAID pain relievers?

No 0 points Yes: 2 points **Points:_____**

Total Points:_____

Evaluation of Patients Risk for serious NSAID-Induced Gastrointestinal event within the next year:

Risk Level	Points	Recommendations
1-No risk	0-10	Patients may use a non-selective formulary NSAID
2-Moderate risk	11-15	Patients may use a non-selective formulary NSAID
3-Significant risk	16-20	<30 days or intermittent use- standard NSAID;>30 days use- salsalate or etodolac*, if failure or intolerant, then COX-2 inhibitor
4-Substantial risk	>20	Use salsalate or COX-2 inhibitor

*Although limited, data does exist supporting etodolac to be a safer alternative to traditional NSAIDs.

Patients with osteoarthritis must fail treatment with acetaminophen 4000 mg daily and/or salsalate prior to initiating a COX-2 inhibitor.

Patients with an allergy to sulfonamides should not receive celecoxib.

Dyspepsia is not a reason to use a COX-2 inhibitor since COX-2 inhibitors may also lead to dyspeptic symptoms.

Lack of response to NSAIDs is not a reason to use a COX-2 inhibitor. COX-2 inhibitors are not more effective than other NSAIDs

The use of low dose aspirin (325 mg qd or less) may reduce or eliminate any GI protective benefit of the COX-2 inhibitors, but did not appear to significantly increase the GI toxicity of NSAIDs (ibuprofen or diclofenac) in the CLASS trial.

Table 3. Monthly Cost of Therapy

Drug	Dose	VA National Formulary (Y/N)	Cost per Month ($)
Acetaminophen	1000 mg qid	Yes	2.40 (500 mg tablet)
Piroxicam	20 mg qd	Yes	1.20
Ibuprofen	800 mg tid	Yes	1.87
Sulindac	200 mg bid	Yes	2.39
Indomethacin	25 mg tid	Yes	2.70
Salsalate	**1500 mg bid**	**Yes**	**2.83**
Naproxen	500 mg bid	Yes	4.23
Diclofenac	75 mg bid	No	5.04-13.20*
Etodolac	300-400 mg bid	Yes	6.90
Tolmetin	400 mg tid	Yes	13.50
Rofecoxib	12.5 -25 mg qd	No 39.00	
	50 mg qd		66.00
Celecoxib	200 mg qd	No 39.00	
	100 mg bid		39.00
	200mg bid		78.00
Nabumetone	750 mg bid or 1500 mg qd	No 48.60	
Misoprostol	200 mcg tid-qid	Yes	41.40-55.20
Misoprostol+Naproxen	200 mcg tid-qid+ 500 mg bid	Yes 45.63-59.43	
Lansoprazole+Naproxen	15 or 30 mg qd +500 mg bid	Yes 33.93	
Famotidine+Naproxen	40 mg bid+500 mg bid	Famotidine-No Naproxen-Yes	77.43

*Generic manufacturer price variation Dose approved only for acute pain. The PBM/MAP criteria for nonformulary use of the COX-2 inhibitors does not permit the use of COX-2 agents for acute pain.

R

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USE OF CYCLOOXYGENASE (COX) 2 INHIBITORS *CELECOXIB (CELEBREX)* OR *ROFECOXIB (VIOXX)* IN VETERANS

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Annotated References: (randomized trials listed in tables 1 and 2)

Fries JF, Spitz PW, Williams CA, et al. A Toxicity Index For Comparison of Side Effects among Different Drugs. Arthritis Rheum 1990;33(1):121-130.

Fries and colleagues developed a morbidity and mortality toxicity index for comparing overall toxicity of groups of drugs. The process of developing this index included identifying techniques for valid assessment of the number of specific toxic events occurring with a drug (numerator) and a valid estimation of the number of years exposed to the drug (denominator). Next, the authors established weights for various adverse effects; determined index structure utilizing weights and severity; and finally, used statistical methodology for fine-tuning and comparison among drugs.

Fries JF, Williams CA, Bloch, DA. The Relative Toxicity of Non-Steroidal Anti-Inflammatory Drugs. Arthritis Rheum 1991;34(11):1353-1360.

The authors discuss a toxicity index (above) that they used to compare 11 different NSAIDs. The toxicity index took into account symptoms, laboratory abnormalities and hospitalizations and weighted them for severity. The most toxic agents were indomethacin, tolmetin, and meclofenamate. The least toxic were coated or buffered aspirin, salsalate, and ibuprofen.

Hawkey CJ. COX-2 Inhibitors. Lancet 1999;353:307-314.

The authors of this review discuss the discovery of the 2 isoforms of COX and screening of drugs for COX-1 versus COX-2 selectivity. All of the COX-2 specific or selective drugs, currently available and in development, are listed.

Lanza FL. A Guideline for the Treatment and Prevention of NSAID-Induced Ulcers. Am J Gastro 1998;93:2037-2046

This review discusses the identification of patients at high risk for NSAID-related GI complications. In addition, the authors talk about strategies for prevention and treatment of NSAID-induced ulcers.

Rothstein R. Safety Profiles of Leading Nonsteroidal Anti-Inflammatory Drugs. Am J Med 1998;105(5A):39S-43S.

The author of this article talks about how newly marketed NSAIDs have tried to utilize special physical or pharmacologic properties to reduce the GI toxicity of NSAIDs. He also discusses how the use of injectable, enteric coating and pro-drug formulations has not provided the desired safety. However, other factors may be involved in decreasing the GI toxicity from NSAIDs including selective COX-2 inhibition, shortened half-life, low or absent enterohepatic recirculation, and nonacidic pro-drug formation.

Singh G, Ramey DR. NSAID Induced Gastrointestinal Complications: The ARAMIS Perspective-1997. J Rheumatol 1998;25 Suppl 51:8-16.

This report is based upon data from the ARAMIS PMS database. This program prospectively follows outcomes, adverse effects, and economic impact of illness in patients with OA and RA. Individuals in this cohort answer questions from the Stanford Health Assessment Questionnaire (HAQ) every 6 months. The questionnaire includes inquiries about medications, side effects, severity of side effects, hospitalizations, emergency department visits, outpatient surgery, and other medical procedures. Patients are contacted until they complete the questionnaire. Questions that are answered in this yearly report are as follows: What are the GI side effects of NSAID use; What is the magnitude of this problem; Are there warning signs for serious GI complications; Who is at greatest risk; Do some NSAIDs cause more GI toxicity than others; and finally, Do H2-receptor antagonists and antacids help prevent serious GI complications?

Wallace JL. Nonsteroidal Ant-Inflammatory Drugs and Gastroenteropathy: The Second Hundred Years. Gastro 1997;112:1000-1016.

This review focuses on both the mechanisms and prevention of NSAID-induced gastrointestinal tract (stomach, small intestine and colon) injury. The authors also discuss new approaches for developing NSAIDs that are safer for the GI tract (zwitterionic phospholipids, pure enantiomers of chiral NSAIDs, NO-releasing NSAIDs, and specific COX-2 selective agents).

Wolfe MM. Future Trends in the Development of Safer Nonsteroidal Anti-Inflammatory Drugs. Am J Med 1998;105(5A):44S-52S.

This review also focuses on the mechanisms and prevention of gastrointestinal injury. The authors also talk about future development of GI-safer NSAIDs (same as above).

Last updated 4/01
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Pharmacology of the GI Tract

Introduction: We will be talking about drugs that affect the GI tract. We will talk about a variety of drugs with different actions like emetics, antiemetics, smooth muscle stimulants, antacids, laxatives, carthartics, anit-diarrheal agents, and drugs used for the treatment of peptic ulcer disease.

I. Emetics
   a. General information:
      i. Use: to induce vomiting after ingestion of toxin, poison, or for drug overdose, or if they have ingested poison. Emetics are to be used if they are not already vomiting.
      ii. These drugs do not have to cross the BBB to cause vomiting. All it has to do is reach the chemoreceptor trigger zone in the area postrema.
   b. Syrup of Ipecac
      i. Route: This is an important difference between syrup of ipecac and apomorophine. Syrup of Ipecac can be taken orally whereas apomorphine is given subcutaneously.
      ii. Onset: Because of the route of administration, it takes about 15-30 minutes to induce vomiting.
      iii. Mechanism:
         1. Act at chemoreceptor trigger zone (same as apomorphine)
         2. Irritates the GI tract
   c. Apomorphine
      i. Route: subcutaneous, therefore it acts much quicker
      ii. Onset: induces vomiting in 2-3 minutes
      iii. Mechanism: act at the chemoreceptor zone to induce vomiting
      iv. adverse effect: can cause repiratory depression.
         1. Don□t give to someone with respiratory difficulties. This side-effect can be countered with naloxone (a morphine antagonist) to block respiratory depression.
   d. Contraindications (for both drugs):
      i. If a strong acid or strong base has been ingested, drug induced emesis can increase the likelihood of esophageal perforations.
      ii. If a patient is comatose or in a stupor, drug induced emesis can increase the risk of stomach contents being aspirated.
      iii. If a patient is over-dosing on a CNS stimulant like strychinine, drug induced emesis can send them into convulsions.
      iv. If a patient has ingested a petroleum distillate (ex: kerosene, gasoline), drug-induced vomiting can cause aspiration of those hydrocarbons and ammonia.

II. Anti-emetics
   a. General Information:
      i. Used to control nausea and vomiting. We have mentioned a couple of these before.
      ii. There are many different neurotransmitters involved in the production of nausea and vomiting. Dopamine, serotonin, Ach, and possibly histamine all seem to be involved
   b. Scopolamine □ absolutely the best drug for the treatment of motion sickness.

i. Mech: antimuscarinic agent
ii. Used to be available orally over the counter but caused lots of side effects: memory loss, dry-mouth, blurred vision, photophobia, tachycardia. Now it is available as a transdermal patch which is suppose to reduce the incidence of side-effects associated with scoloplamine.
iii. Will still cause some side-effects, but not to the same extent as if taken orally.
iv. Will also cause sedation

c. Antihistamines
   i. Cyclizine
   ii. Diphenhydramine (BENEDRYL)
      1. Use: treatment of motion-sickness.
      2. Both of these are available over the counter
      3. Mechanism: their anti-emetic effects may be due the blocking of histamine action, but more likely, it is their scopolamine-like activity (i.e. anticholinergic) that produce the anti-emetic action.
      4. adverse effect: sedation (like scopolamine)
      5. Not as effective as scopolamine

d. Drugs used to prevent nausea caused by anticancer drugs
   i. Metoclopramine
      1. Mech: controversial. However, generally believed to be a dopamine antagonist
      2. Use: prevention of nausea caused by anticancer drug cisplatin (for other uses, read on)
      3. dopamine antagonist
      4. Some people believe that it stimulates Ach release, and others believe that it sensitizes the Ach receptors to the Ach.
   ii. Odansetron
      1. Mech: serotonin antagonist (5-HT3)
      2. Use: probably the best drug for the control of nausea & vomiting associated with other anticancer drugs.

e. We know that there must be a number of neurotransmitters involved in producing nausea and vomiting. We know that Ach, Dopamine, histamine, and serotonin all are involved because the above drugs target these molecules or their receptors.

III. Smooth Muscle Stimulants
   a. General Information:
      i. Can be used for:
         1. Gastric atony - as long as there is no obstruction, otherwise, these drugs cause GI tract perforation.
         2. Reflux esophagitis □ Acidic stomach contents can move into the esophagus if the tone of the lower esophageal sphincter (LES) is not great enough. When this happens, you get a burning sensation because the esophagus is poorly protected by mucous relative to the stomach. This produces a heartburn kind of pain. We will be discussing numerous drugs used to treat this condition.
         3. Therapeutic approach:
            a. Some drugs will increase the tone of LES,
            b. some will neutralize the acid
            c. stop acid production altogether.
            d. H. pylori is thought to be the cause of a lot of reflux esophagitis. Antibiotics against this bacterium are now being used to treat this problem.
   b. Bethanecol □ muscarinic receptor agonist
      i. Mechanism: stimulated GI tract motility and increases the tone of LES; also increases HCl secretion (this is an adverse effect); bladder atony
      ii. Uses: see above

iii. Positively charge. Thus, it does not have any central effects.
iv. adverse effect:
1. stimulates HCl secretion- so you will not want ot use this on someone with a peptic ulcer
2. bronchial constriction (since muscarinic receptors are also found on the bronchial smooth muscle, acetylcholine-like drugs and cholinesterage inhibitors cause bronchial constriction if the drugs can reach the site).

c. Metoclopramide □ dopamine antagonist
i. Mechanism:
1. Stimulation of GI motility: Blocks action of dopamine on certain autonomic ganglia thus inhibiting the slow inhibitory potential. This will increase the activity of the post-ganglionic parasympathetic nerve terminal and lead to an increased Ach release.
2. There is no increase in HCl
ii. Uses: see above. Also, an anti-emetic. A better drug than Bethanecol for people who have peptic ulcers.
iii. Contraindication:
1. pheochromocytoma □ This is a tumor of the adrenal medulla that releases huge amounts of NE & Epi into the system without stimulation of nicotinic cholinergic receptors. You will see high blood pressure. Metoclopramide will aggravate this by stimulating the release of Epi & NE out of the adrenal medulla. The exact mechanism of this stimulation is unclear. The theory goes: Besides having anti-dopamine effects, metoclopramide also sensitizes muscarinic receptors to the action of Ach. Nothing is said about nicotinic receptors though, so again, the mechanism is unclear.
2. Metoclopramide can cross the blood-brain-barrier
a. Central side effects can occur
d. Bethanechol vs. Metoclopramide
i. Metoclopramide is not charged; Bethanechol is charged. Hence, metoclopramide can cause drowsiness
ii. Metoclopramide does NOT stimulate HCl secretion. Hence if a patient has both reflux esophagitis and peptic ulcer disease, you would give that patient metoclopramide instead of bethanecol.
iii. Bethanecol has the tendency to cause gastric distress or diarrhea; metoclopramide is much less likely to show these adverse effect especially in patients being treated for reflux esophagitis

IV. Antacids and anti-secretory drugs
a. General Information:
i. Antacids have been around for a long time, and 4 of them will be discussed here. Some of these antacids are making a comeback in the peptic ulcer area. He wants us to remember that it is an important topic to keep up with since the drugs used in this area changes frequently.
ii. All of the duodenal ulcers are associated with excess HCl
iii. 50% of the gastric ulcers are associated with excess HCl
iv. The other 50% of the gastric ulcers are NOT associated with excess HCl. As a matter of fact, these ulcers may show a decrease in HCl production than normal.
v. Type I ulcers □ The gastric ulcers that is NOT associated with excess HCl. It is believed that bile salts reflux into the stomach causing an erosion of the mucosal layer making the tissue more sensitive to the action of acid and pepsin.
vi. You don□t want to use antacids in situations where excess HCl is NOT being produced. In these instances, there would not be any benefit in using the antacid, and the ulcer might even be aggravated. (they also cause acid rebound)
V. Causes of ulcers (3 of them):

a. Helicobactor pylori theory:
   i. 100% of the duodenal ulcers is caused by Helicobactor pylori. Duodenal ulcers are the most common type of ulcers. However, Dr. Carroll see a flaw in the H. pylori theory in that someone can have elevated population of H. pylorus and NOT have duodenal ulcer. Thus, there isn□t a perfect correlation between H. pylorus and duodenal ulcer.
   ii. What about H. pylori association with other ulcers or diseases?
   iii. 50% of the gastric ulcers that produce too much HCl (type II ulcers)□ has not been firmly established.
   iv. Reflux esophagitis □ has not been established, but the possibility is there.
   v. A typical treatment regimen for duodenal ulcers believe to be caused by H. pylori:
      1. (1) bismuth (aka pepto-bismol), (2) tetracycline, (3) ranitidine, (4) metronidazole (aka Flagyl).
      2. Duration of treatment is a couple of weeks.
      3. This combination does an excellent job of eradicating the bacteria with very little ulcer relapse.
      4. They used to tell medical students that stress-induced acid production (all day long) is the most important cause of duodenal ulcers. Well, this went □out the window□ with the discovery of H. pylori, although Dr. Carroll thinks that stress does play a role. These bacteria thrive in a low pH environment, so if you stop HCl production, they don□t multiply as well. If you have a duodenal ulcer, the best regime of treatment is the drug mentioned above + quit smoking + don□t drink excessively.

b. Chronic Non-Steroidal Anti-Inflammatory Drug (NSAIDs) usage: such as aspirin
   i. Second most common cause of ulcer.
   ii. Why would you give someone aspirin to treat rheumatoid arthritis if there are other drugs like **COX2** inhibitors (celecoxib) that you can give that won□t cause peptic ulcer disease?
   iii. Because selective **Cox2 inhibitor** is not effective in every patient. In these instances where selective **COX2** inhibitors are not helpful, then aspirin must be used even though high doses are required.
   iv. There is another situation when high doses of aspirin is being called for: Transient ischemic attack (TIA) (stroke)□ if you take one baby(?) aspirin every other day, it will protect you from a stroke or transient ischemic attack. At these low dosages (60mg-80mg of aspirin every other day), it is not enough to give you peptic ulcer disease. However, the president of the American Heart Association has published papers recently indicating that pretty high doses of aspirin is actually required to provide protection from TIA (more like 1300mg per day). This is equivalent to 4 Bayer aspirins a day. Of course, this 1300mg per day is more for people who have already had a TIA than someone who never had. In any case, this level of aspirin is likely to cause peptic ulcers.
   v. We do have a drug available though called misprostol (cytotec) that will prevent the development of an aspirin-induced ulcer. This is only useful BEFORE the development of the ulcer if taken concurrently with aspirin. This drug stimulates the production of mucus and this helps in a preventative fasion.
   vi. There is also new studies that have shown linkage between Alzheimer□s and the use of Aspirin.

c. Zollinger-Ellison Syndrome
   i. Least common cause of ulcer.
   ii. Can be life-threatening
   iii. This disease is caused by gastrin-producing tumor cells that make a tremendous amount of gastrin which stimulates Histamine to be released. Histamine then stimulates the H2 receptor and an increase in acid production occurs.
   iv. Treatment: Omeprazole (Prilosec) □ this drug completely shuts down (100%) HCl production from parietal cells.
   v. Remember that both histamine and Ach will stimulate HCl production. So if you inhibit just histamine or just Ach, you won□t totally shut down acid production. However, a drug like omeprazole that stops the K+/H+ ATPase (he said □Na/K ATPase□, but I think that□s wrong) will totally shut it down. (pg 237 Pharm Lippincott)

VI. Antacids

a. Again, antacids are not recommended as treatment of gastric ulcers.
   i. However, you can use antacid to reduce the pain of a peptic ulcer on a temporary basis until a diagnosis can be made to determine if someone has H. pylorus.

1. How to diagnosis H. pylorus ulcers
   a. A breath test is available for detection of H. pylori. These Gram-negative bacteria produce urease, so if someone drinks urea (yuck!), the urease will break urea down into CO2, which is then measured. This is how you determine if there is an excess population of H. pylori in the duodenum.

2. Two of the antacids (aluminum hydroxide, magnesium hydroxide) are believed to cause healing of ulcers whether than just neutralizing the acid and reducing the pain. Hence, if you had to give antacid to a patient who may have an ulcer, it would be better to use one of these two that promote healing.
3. Some antacids are also used for reflux esophagitis □ they will increase the tone of LES.
   a. NOTE: Some antacids will increase gastric emptying while others will decrease gastric emptying. An antacid (aluminum hydroxide) that decreases gastric emptying would not be good to use with reflux esophagitis because it will keep the acidic contents in the stomach making more available to move into the esophagus.

ii. Major problem associated with all antacids: You have to take them numerous times throughout the day because of □acid rebound□ □
1. Remember, gastrin-producing cells are inhibited by low pH and stimulated by high pH. Thus, when antacids raise the pH of the stomach, gastin is released. Gastrin will cause the secretion of more HCl and at the same time stimulate the secretion of histamine. Histamine will then potentiate the effect of gastrin causing even more HCl release.
2. So when you neutralize the acid, eventually, there will be a greater increase in the secretion of HCl from parietal cells to counter the neutralization.
3. In the end, you will have to take antacid seven or eight times a day.

b. The nonsystemic antacids - they are not appreciably absorbed into the system.

i. Aluminum Hydroxide
1. Weakest non-system antacid. Raise pH to about 4 or 5.
2. Will slow gastric-emptying rate:
3. Pros: slows acid delivery to the duodenum.
4. Cons:
   a. If additional drugs are being taken, their delivery to the duodenum is slowed - - which will delay onset of action for that drug.
   b. Again, you do not want to use this to treat reflux esophagitis because of this slowing of gastric-emptying rate. This will cause more acid to have access to the esophagus
5. adverse effect: Constipation
6. Use: as an antacid (see above), treatment of diarrhea
7. Causes healing of ulcer (because of the aluminum)

ii. Calcium Carbonate
1. More potent than aluminum hydroxide (raise pH higher to around y)
2. Considered a non-systemic antacid even though calcium can be absorbed if someone is drinking lots of milk that which coats their stomach.
3. Calcium may cause gastrin release and HCl release.
4. Increases gastric-emptying rate
5. Acid rebound might be even more severe here.

iii. Magnesium Hydroxide (milk of magnesia)
1. Most potent; raises pH to around 9

2. Considered a non-systemic antacid, but some magnesium is absorbed. Hence this is contraindicated in patients with renal difficulties. Magnesium can inhibit renal enzymes.
    a. If a person has renal problems, you do not want them using magnesium Hydroxide. Magnesium can depress renal enzyme activity
3. Have healing properties
4. Increases gastric-emptying rate
5. adverse effect: caused diarrhea, increases gastric-emptying rate
6. If you take a combination of magnesium hydroxides and aluminum hydroxide: does not show either constipation or diarrhea adverse-effects. They will neutralize each other.

c. Sodium Bicarbonate (alkazeltsor)
    i. Raises pH to around 9
    ii. The only system antacid listed. Hence, it will be absorbed into circulation in significant amounts, leading to an increase in blood volume and an increase in urinary pH
    iii. Hence sodium bicarbonate is not very good for CHF patients or patients with hypertension, or patients taking:
        1. Weak organic acid - normally not ionized in acidic urine, but will now be ionized and not reabsorbed.
        2. Weak organic bases - normally should be ionize in urine, but now will not. They will be more readily reabsorbed into body instead.
        3. The sodium will increase blood volume, and then blood pressure.
    iv. A change in stomach pH will also alter drug absorption, particularly affecting weak acid. In the more basic environment, the weak acids will ionize therefore not be absorbed readily so that the drug□s action will be delayed.
        1. Examples of this are the amphetamines. If you take amphetamines while taking sodium bicarbonate, you get a much greater effect because the amphetamines are not cleared as fast.

VII. Anticholinergic Drugs

a. Atropine □ non-selective muscarinic receptor antagonist
    i. Not good to use for the treatment of peptic ulcer by itself because it doesn□t totally shut down HCl secretion (remember that histamine is also involved in this process and not just Ach).
    ii. Slows GI tract motility □ helpful in reducing the pain
    iii. Adverse effect: A lot of them, including dry-mouth, blurred vision, photophobia, tachycardia, anxiety, etc.
b. Pirenzepine □ selective antimuscarinic 1 receptor antagonist
    i. Widley used in Europe, but we skipped due to lack of class time.

c. Methantheline & Propantheline
    i. Action:
        1. Have atropine-like activity, hence they also block acetycholine muscarinic receptor sites.
        2. Ganglionic blockers □ blockage of ganglionic transmission causing a reduction in GI motility and HCl secretion. (Again, reduction in GI motility is helpful in relieving ulcer pain).
    ii. These drugs are used chronically despite their nasty side-effects: orthostatic hypotention, impotence, blurred vision, photophobia, in general, impairs your body from maintaining homeostasis.
    iii. Use: Irritable Bowl Syndrome, Peptic Ulcer Disease (There are better drug to use than these two; however, if a patient□s peptic ulcer pain is not relieved with other medications, than methantheline or propantheline may be indicated).

VIII. H2 Receptor Antagonists (cimitidine, ranitidine, nizantidine, femotidine)

a. There are 4 of them, and all have the exact same mechanism of action: block H2 receptors on parietal cells. Since these drugs have no action at the H1 receptors, they are not effective in the treatment of allergic rhinitis and such.
b. Use: adjunct drugs during H. pylori induced Duodenal ulcer (Ranitidine, as part of the 4 drug regimen mentioned earlier), gastric ulcers involving excess HCl secretion, reflux esophagitis, Zollinger-Ellison Syndrome
c. The basic difference between the 4 drugs: the degree to which they depress liver microsomal enzyme activity
d. Not all HCl production is blocked because Ach acts on the muscarinic receptors to stimulate HCl secretion. Histamine is more important than Ach, but it is NOT the only player.
e. Suppression of liver microsomal enzymes leads to potential interactions with drugs like warfarin and phenytoin that are heavily metabolized by these enzymes.
    i. Cimetidine (Tagamet):
        1. First one developed.
        2. Does not create acid rebound □ this is its greatest advantage over Antiacids.
        3. It has the most side effects, including loss of libido in males
        4. Greatest effect of the H2 antagonists is that it depresses the liver microsomal enzyme activity: therefore, get greater potential for interaction with drugs metabolized by this system, (phenytoin, warfarin, etc.)
            a. Because Warfarin will not be metabolized as readily, you must watch the doses given.
        5. Reduces hepatic blood flow: can have an effect on other drugs metabolized by the liver in a first-pass situation
        6. Crosses the blood brain barrier more readily than other H2 blockers: can cause some CNS side effects including sleepiness, especially in elderly.
        7. Reportedly depresses alcohol dehydrogenase activity: shares this affect with ranitidine. This means that alcohol will have a greater effect.
    ii. Ranitidine (Zantac):
        1. Fewer side effects than cimetidine
        2. Less potential for liver microsomal enzyme depression, but there still is a depression and may depress alcohol dehydrogenase system (up to 40% -arguable statistic), so effects of alcohol will be intensified if pt is on Zantac.
        3. Slightly more effective for reflux esophagitis than cimetidine
        4. Better for treatment of Zollinger-Ellison syndrome than cimetidine □it totally shuts down HCl production
        5. Does not cross blood brain barrier (BBB) as readily as cimetidine: causes less sleepiness or loss of libido in males.
        6. Ranitidine, is used as part of the 4 drug regimen mentioned earlier
        7. Usually the H2 blocker of choice for combination treatment of duodenal ulcers is with bismuth, amoxicillin, TCN, or Flagyl. This is probably only because physicians have had more experience with it than other H2 blockers.
    iii. Famotidine (Pepcid) & · Nizatidine (Axid):
        1. They have the same mechanism of action with a slightly different degree of efficacy (not thought to be of any greater efficacy than ranitidine).
        2. Do not affect liver microsomal enzyme system at all: won□t interact w/ other drugs metabolized by this system.
        3. Treatment of gastric ulcers involving excess HCl secretion: Type II ulcer in the stomach. Not used for Type I ulcers, which are not caused by excess HCl secretion.

IX. Bismuth (Pepto-Bismol)

a. A □mainstay□ antibacterial drug in the treatment of duodenal ulcer caused by H. pylori & other Gram (-) bacteria (along with TCN and amoxicillin). By itself, it is only effective in 30% of patients. There are questions as to its efficacy □ it probably has a short life for being a recommended treatment for H. Pylori ulcers.
b. Very good treatment of travelers□ diarrhea, which is usually caused by E. coli. It□s better if used prophylactically (as compared to stopping diarrhea) before traveling outside of the US. It is also sometimes in combination with an antibiotic such has ciprofloxacin (Cipro). This is used to prevent □travelers diarrhea□
c. Side effects
    i. Causes ringing of the ears
    ii. Turns stool black

X. H. Misoprostol (Cytotec)
   a. Prostaglandin (PGE1) analog, which is believed to increase gastric mucus production and decrease HCl secretion.
   b. Used to prevent development of ulcers in patients currently taking NSAIDs such as aspirin or indomethacin. There is argument of effective aspirin doses for prevention of transient ischemic attacks □ some say 60-80mg qd, others (American Heart Association) say 1300mg qd is appropriate□40-50% of cardiologists follow this recommendation.
   c. Not useful if ulcers already exist.
   d. Side effects:
      i. Diarrhea: from increased GI motility
      ii. Increases uterine contractions: absolutely contraindicated in pregnant women, because it can cause spontaneous abortion.

XI. □Acid Pump□ Inhibitors (fairly new drugs): Omeprazole (Prilosec, aka Losec) and Lansoprazole (Prevacid)
   a. Same mechanism of action: inhibit the sodium-potassium ATPase pump at the parietal cell
   b. Totally shuts down HCl production with a single dose per day: compared to H2 receptor antagonists which only partially stop HCl production.
   c. Used on an acute basis more than a chronic basis b/c of changes in natural (and necessary) flora.
   d. A comparison in efficacy of treatment of H. pylori induced duodenal ulcer: Omeprazole + amoxicillin was equally effective to the bismuth + TCN + ranitidine + Flagyl
   e. Preferred tx for reflux esophagitis rather than H2 receptor antagonists □totally blocks HCl production
   f. Treatment of choice for Zollinger-Ellison syndrome where massive gastrin production from a tumor leads to massive HCl production that can possibly be life threatening.
   g. These drugs are being tested with the combined use of antibiotics to treat duodenal ulcers. The combination of Amoxicillin and Omeprazole is just as effective as the Bismuth, Ranitidine, Tetracycline, metronidazole combination.
   h. Side-effects:
      i. Rashes
      ii. Depression of liver microsomal enzymes
      iii. Omeprazole vs. Lansoprazole in efficacy and production of side effects is yet to be determined. All we know is that they have the same mechanism of action and are roughly equivalent in their efficacy.

XII. Antidiarrheal Agents
   a. Diarrhea can result from a variety of causes including:
      i. Pancreatitis: fats, proteins, CHO not being metabolized therefore retaining water and giving diarrhea
      ii. Traveler□s diarrhea: irritation of GI tract from bacteria
      iii. Carcinoid tumor
   b. Opiates (main group of drugs used to treat diarrhea). Reduce ACh release from postganglionic parasympathetic nerve terminals that innervate GI tract. This decreases motility and allows more time for water and electrolyte reabsorption to occur. These drugs have exactly the same method of action.
      i. Side effects - Opiates cause histamine release from mast cells and may cause itchy skin
      ii. Contraindications: If Salmonella (food poisoning) is the cause of the diarrhea. Opiates will contain the bug in the body.
      iii. The Drugs:
         1. Diphenoxylate: meperidine (Demerol) analogue
            a. Acts on peripheral receptors to reduce diarrhea but it crosses the BBB and acts on central opiate receptors produce euphoria □ has high abuse potential.
            b. Combined with atropine (Lomotil): reduces euphoria, but has side effects: anxiety, dry mouth, tachycardia, blurred vision.
         2. Loperamide (Imodium): now available OTC

a. Does not cross BBB and act on CNS opiate receptors, so no abuse potential
b. Theoretically as good as Diphenoxylate (questionable)

3. Octreotide □for treatment of carcinoid syndrome w/intense diarrhea. There is production of excessive serotonin, bradykinin, & somatostatin in the GI tract by a tumor, which causes very intense diarrhea. Treat it with Octreatide (a somatostatin analogue) to stop diarrhea. The actual reasons for this working are not completely understood.

XIII. General Pharmacological Considerations: drugs that affect the GI tract have potential for interaction in simultaneous administration.

a. Drugs that slow the rate of gastric emptying: remember, most drugs are absorbed in the duodenum; thus, onset of action of such drugs will be delayed
b. anticholinergics (atropine, propantheline, methantheline);
   i. AlOH3 antacid
   ii. Opiates
c. Drugs that increase the rate of gastric emptying, may increase the onset of action of other drugs absorbed in the duodenum
   i. Bethanachol
   ii. Metaclopromide
d. Antacids other than AlOH3
   i. Digoxin: large particle size, so requires a long time in the stomach to be dissolved. If it does not undergo dissolution and enters the duodenum, it will not be absorbed. Drugs that increase gastric emptying will decrease the bioavailability of Digoxin.
   ii. Drugs that chelate Tetracyclin: Ca, Mg, and Al antacids and sucralfate.
   iii. Since TCN is used for treatment of duodenal ulcers, these drugs will prevent adequate treatment.

XIV. Questions on Test Questions

a. Know the material from notes/lecture. You should not have to look in the book for additional information on the test. It all can be found in the handouts and class notes.
b. These test questions are designed so that 4 answers are clearly wrong, and one is clearly right.
c. Both names of the drugs will be given. You will see the drug name as well as the trade name.

FLAVONOIDS

Flavonoids, of which there are over 4,000, are plant pigments which provide color to many fruits and flowers. They have anti-allergic, anti-inflammatory, antiviral, and anticarcinogenic properties.

Flavonoids are of great importance because of their antioxidant functions. A 1993 study reported a high intake of flavonoids was associated with a decrease in fatal heart attacks.1 When heart attacks did occur, **flavonoid** levels were low. It is speculated that they protect the heart by preventing cholesterol oxidation. Flavonoids are believed to be even more powerful antioxidants than Vitamin C, Vitamin E, selenium, and zinc.2

Catechins:

Catechins are naturally occurring flavonoids containing some of the properties of silymarin and lipoic acid. As an antioxidant, they inhibit free radical oxidative damage.

Red Wine Extract:

Red wine and the skins and seeds of red grapes contain **flavonoid** compounds which contribute to good health. These flavonoids include catechins, proanthocyanidins, and anthocyanidins. Younger red wines will have more flavonoids. White wines have very few. There are supplements similar to Pycnogenol made with grape extract rather than pine bark. Studies have indicated that certain components of red wine appear to offer protection from heart disease by increasing the good HDL cholesterol. These compounds (the polyphenols and flavonoids) also reduce the chances of blood clots.

Green Tea: *(Camellia sinensis)*

Green tea contains good amounts of Vitamins C; E, minerals, polyphenols, and flavonoids (catechin epigallocatechin gallate-EGCG). Green tea polyphenols are hailed for their antioxidant functions. They are thought to increase antioxidant functions of other enzymes as well. A clinical study with human subjects confirmed the role of this **flavonoid** in cancer prevention. It has shown most beneficial in gastrointestinal cancers, and cancers of the lung and breast. A 1993 study reported the action of green tea polyphenols in inhibiting carcinogenic nitrosamines when taken with meals. The common consumption of green tea with meals in Japan has been linked to a much lower cancer rate in this country. Green teas are thought to have little to no side effects.

Research indicates green tea kills viruses and bacteria and acts as an immunity booster and antioxidant. There is speculation that green tea may be a potential treatment for cancer, heart disease, and dental cavities. In addition to tea form, there are green tea extracts in capsule form. Results from animal studies indicate that green tea can prevent skin cancer. There is also some evidence that the compounds in this supplement protect against lung, liver, pancreatic, and stomach cancer. The benefits of green tea in heart disease have also been noted. One study found that Japanese women who drank at least five cups of green tea a day lowered their risk of stroke by half. Other studies indicate that green tea can lower cholesterol and blood pressure. In addition to its benefits against degenerative disease, green tea has also been utilized as a weight loss aid.

Quercetin

Quercetin is the most active **flavonoid** group in experimental studies. Quercetin acts as an antiviral, anti-inflammatory, antioxidant, and a Vitamin C preserver. Its anti-inflammatory and anti-allergic

properties make it beneficial for arthritis and hayfever.

Quercetin offers relief for diabetics by inhibiting the enzyme aldose reductase. This enzyme converts glucose to sorbitol, which is associated with several diabetic complications. Also important for diabetics is quercetinÕs ability to enhance insulin secretion, ward off free radical activity in pancreatic cells, and obstruct platelet aggregation.

Quercetin prevents the buildup of sorbitol in the lens of the eye, there by delaying the development of cataracts. The antitumor effect of quercetin is perhaps its greatest function. Though only tested in animals and in *in vitro* studies, quercetin has been shown to be active against many types of cancers. Researchers have also found quercetin inhibits DNA synthesis in leukemia cells. It was found to be dose related Ñ the higher the dose of quercetin, the more leukemia-cell DNA synthesis was slowed. After two or three days, high doses completely inhibited DNA synthesis. DNA synthesis resumed in the cells after quercetin was removed.

Citrus Bioflavonoids

Citrus bioflavonoids include rutins, hesperidin, quercetin, and naringin. These are the most used and least expensive of **flavonoid** preparations. However, they are also the least active. Citrus bioflavonoids are needed for the proper absorption and use of Vitamin C. They have been successful in the treatment of capillary permeability, easy bruising, hemorrhoids, hypertension, and varicose veins.

Proanthocyanidins

Proanthocyanidins (PCOs) are among the several groupings of flavonoids. PCOs are found in many plants and red wine. Commercially these flavonoids are available as grape seed extract and pine bark extract. PCOs are beneficial for increasing intracellular levels of Vitamin C, protecting the integrity of capillaries and collagen, and working as an antioxidant. Research from 1993 indicates these flavonoids inhibit substances such as histamines which cause inflammation and allergies. In addition to use in vein and capillary disorders, PCOs are also indicated in retinal disorders. A 1988 study conducted on humans found grape seed extract improves visual function in healthy subjects.

Hawthorn

Hawthorn *(Cratageus oxyacantha)* is a native European plant. It contains polyphenols and the flavonoids quercetin, vitexin, catechin. Research indicates that this herb lowers cholesterol and blood pressure, and can help prevent heart palpitations and arrhythmias. Because it has such effects on the heart, it is advisable to use only under a physicianÕs supervision.

Pine Bark/ Pycnogenol

Pycnogenol[a] is a trademark for a blend of nutrients extracted from the bark of the coastal pine tree *Pinus maritima*, which is native to France. The bark is rich in flavonoids, particularly the proanthocyanidins. It has proven to be a powerful antioxidantÑmore powerful than Vitamin E and Vitamin CÑin fat and water-based surroundings.

Pycnogenol does more than protect. It also helps repair. It can strengthen blood vessels and reduce vascular fragility, improve circulation and vision, improve skin smoothness and elasticity, improve joint flexibility and fight inflammation. Because of its antioxidant properties, it is used to prevent of cancer, heart disease, and other degenerative conditions. The collagen-rich connective tissue in artery walls is protected and stimulated for repair by Pycnogenol, which in part helps protect against early atherosclerosis. It also reduces histamine production, thereby helping artery linings resist attack by mutagens, free radicals and oxidized LDL-cholesterol.

Healthy brain cells are important for memory and stroke prevention. Strengthened capillaries help protect against stroke. Besides protecting and strengthening blood vessels, Pycnogenol is able to cross the blood-brain barrier to protect the brain from free radicals. This protection will help memory and reduce senility. It appears even sluggish memories are improved perhaps due to better circulation and cell nourishment.

Researchers at the Second International Pycnogenol Symposium, held in May 1995, reported the effective

use of the supplement in attention deficit disorder (ADD). Many patients formerly on Ritalin have switched to Pycnogenol and had much success.

Milk Thistle

Milk thistle *(Silybum marianum)* is a very popular supplement in Europe, particularly Germany. The standardized extract silymarin contains flavonoids which provide special protection to the liver. Milk thistle acts as an antioxidant which encourages the regeneration of liver cells and enhances the ability of this organ to filter toxins from the blood.5 This supplement is used in the prevention and treatment of toxin exposure (food poisoning, industrial chemicals, radiation, alcohol and drug poisoning).6 It is also used as a general immune stimulant.

Soy

Soy foods contain two particularly beneficial isoflavones, genistein and daidzein. These isoflavones have notable implications in the prevention of various cancers and heart disease. Studies also point to isoflavones as effective hormone balancers in women and potential prevention against osteoporosis.

Genistein and daidzein work as antioxidants, inhibiting the free radicals responsible for the development of cancer and heart disease. These compounds contribute to a healthy heart by preventing the causal factors of atherosclerosis such as reducing platelet aggregation and plaque formation, lowering cholesterol levels and improving artery elasticity. Populations with a higher consumption of soy foods have been found to have a lower risk of breast, colon, and prostate cancer, and cardiovascular disease rates than those with less soy in the diet.

Phytoestrogens have the ability to bind to estrogen receptors of cells in the body, and block some of the human estrogen circulating in the body from getting to these cells. Blocking estrogen, and thus lowering estrogen levels, may reduce side effects or toxicity of excessive estrogen levels on the body. These isoflavones are thought to be effective against breast cancer because they can also attach to estrogen-receptive tumors and prevent their growth.

Rutin

Last but not least, rutin is a **flavonoid** which improves circulation in the lower limbs. It has been used in treating varicose veins and hemorrhoids.